intensity) 51.1 (100), 77.1 (57), 78.1 (77), 106.1 (83), 180.1 (74); ^{1}H NMR ($CDCl_3$) δ 7.16 (d, 1 H), 6.74 (m, 2 H), 4.35 (t, 2 H), 4.15 (br s, 1 H), 3.49 (t, 2 H); IR (KBr) 3400, 1550, 1352, 1325, 1221, 1120, 1042, 840, 731, 720 cm^{-1}. Anal. Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.48. Found: C, 52.87; H, 4.49. The several other products observed by TLC were present in insufficient quantity to enable identification. Several other runs were conducted with longer irradiation times and different workup procedures, but the results did not differ substantially from those reported above. The yield of **7** observed in two other runs was 7.8%, and those of **4** were 9.2% and 13.8%. A portion (1.0 mL) of the final irradiated solution was extracted with ether (1.0 mL), and the extract was subjected to GC/MS analysis; no trace of a peak appeared having a molecular ion at *m/e* 135, which would correspond to 3,4-dihydro-2*H*-1,4-benzoxazine.

A run conducted as above at pH 9.5 on the hydrochloride of **1** (0.917 mmol) in the presence of 1 equiv of 3,5-dinitrobenzoic acid gave 0.357 mmol of unreacted **1** (as thermal Smiles product **4**), 0.010 mmol of reaction product **4**, and 0.318 mmol of **7**. The yields of **4** and **7** based on 0.560 mmol of reacted **1** are 18% and 57%, respectively.

Preparative Irradiation of 1-Amino-2-(4-nitrophenoxy)-ethane (3). The hydrochloride of **3** (0.600 g, 2.74 mmol), dissolved in 550 mL of Na_2CO_3 (0.04 M) which had been adjusted to pH 10, was irradiated through a Pyrex filter for 1.5 h with a 450-W mercury lamp. The temperature initially was maintained at 0 °C by immersing the reactor in an ice bath; the temperature rose to 16 °C during the first 0.5 h of irradiation and stabilized at about 18 °C. The final reaction solution was neutralized (pH 7) and extracted with six 100-mL portions of EtOAc. The organic phases were combined, dried over $MgSO_4$, and concentrated to a reddish brown oil (0.392 g), which was applied in EtOAc to a column of alumina (15 g) packed in ether. Fractions of 30 mL were collected as the eluting solvent was gradually changed to EtOAc, then MeOH, and then water. Fractions 1 and 2 (ether eluant) contained a red solid (0.067 g, mp 100–107 °C) identified as 6-nitro-3,4-dihydro-2*H*-1,4-benzoxazine (**8**) (14%) by comparison with an authentic sample.[24] Fractions 4 and 5 (ether eluant) contained a yellow solid (0.055 g, mp 110.5 °C) identified as *N*-2-hydroxyethyl)-4-nitroaniline (**6**) (11%) by comparison with an authentic sample.[23] Fractions 13 and 14 (methanol–water eluant) contained a red solid (0.148 g) identified as the sodium salt of *N*-(2-hydroxyethyl)-2-hydroxy-5-nitroaniline (25%) by comparison with an authentic sample.[25] Other runs of this preparative reaction which used slightly different irradiation conditions and workup procedures gave results similar to those noted above.

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Registry No. **1**·HCl, 98395-65-4; **2**·HCl, 61711-97-5; **3**·HCl, 98395-62-1; **4**, 4926-55-0; **5**, 55131-09-4; **6**, 1965-54-4; **7**, 98395-66-5; **8**, 28226-22-4; **9**, 74032-78-3; 4-$NO_2C_6H_4OCH_2CH_2OTs$, 22483-44-9; 3-$NO_2C_6H_4OCH_2CH_2OH$, 16365-26-7; 3-$NO_2C_6H_4OH$·Na, 3019-85-0; $ClCH_2CH_2OH$, 107-07-3; 3-$NO_2C_6H_4OCH_2CH_2OTs$, 98395-63-2; $BrCH_2CH_2Br$, 106-93-4; 2-$NO_2C_6H_4OH$·Na, 824395; potassium phthalimide, 1074-82-4; *N*-(2-(4-nitrophenoxy)ethyl)-pthalimide, 98395-61-0; *N*-(2-(3-nitrophenoxy)ethyl)phthalimide, 58910-41-1; *N*-(2-bromoethyl)phthalimide, 574-98-1; *N*-(2-(2-nitrophenoxy)ethyl)phthalimide, 98395-64-3.

Thermal Rearrangement and Decomposition Products of Artemisinin (Qinghaosu)[1]

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Artemisinin (qinghaosu, **1**), a clinically useful antimalarial agent isolated from the plant *Artemisia annua*, is an unusual sesquiterpene lactone which contains an epidioxide (peroxide) function. It is surprisingly stable in neutral solvents heated up to 150 °C or neat, up to 50 °C above its melting point (156–157 °C) for 2.5 min. Extensive changes are detected, however, after 10 min at 190 °C. One decomposition (**2**, 4%) and two rearrangement (**3**, 12%, **4**, 10%) products were isolated by silica gel column chromatography. The structures of the products were characterized by IR spectroscopy, CIMS, ^{1}H NMR, ^{13}C NMR, and X-ray crystallography. The mechanism that accounts for the formation of these products involves the homolytic cleavage of epidioxide to generate a free radical intermediate which rearranges or decomposes to give the observed products.

Artemisinin (qinghaosu, **1**), a clinically useful antimalarial agent isolated from *Artemisia annua*, is an unusual sesquiterpene lactone which contains an epidioxide (peroxide) function.[2-6] In the course of developing a GC/MS assay method to be used in pharmacokinetic studies, it was necessary to examine the thermal stability of the com-

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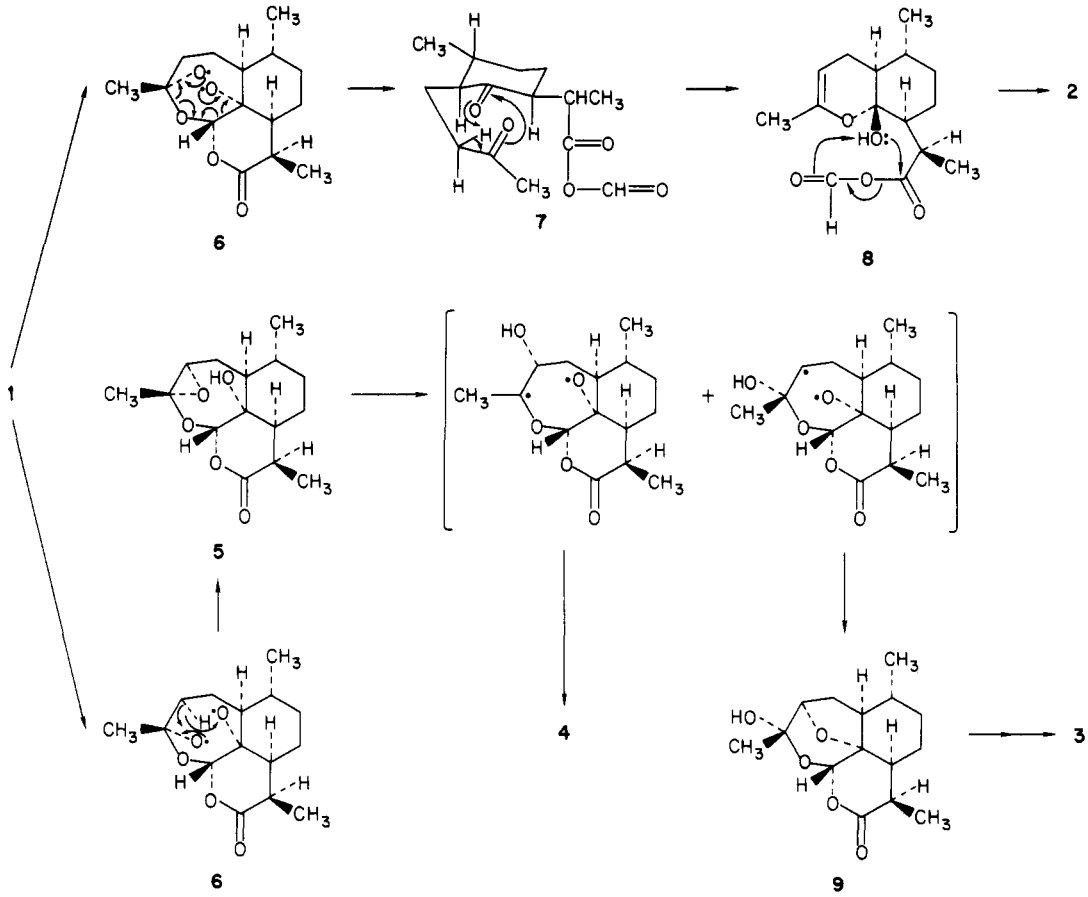
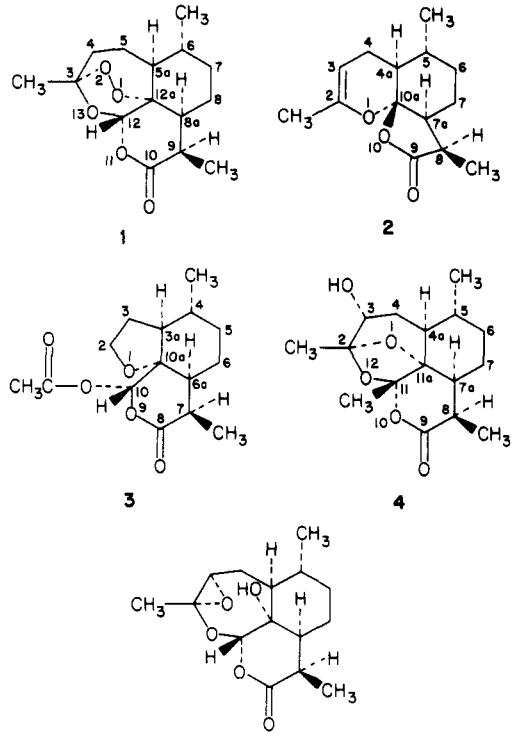
Scheme I



pound and to identify its degradation or rearrangement products. Artemisinin has been reported to be labile to acidic or basic treatment, but unexpectedly stable in neutral solvents heated up to 150 °C.[7] We have found that artemisinin is unaffected by heating neat for about 2.5 min at 200 °C, i.e., about 50 °C above its melting point (156–157 °C,[2] 153–154 °C[8]); but extensive changes were detected if heating was extended beyond approximately 3.5 min.

Compound **1** was heated with stirring in a flask without solvent in a silicone oil bath at 190 °C for 10 min, and the products were separated on a silica gel column using 7.5% EtOAc–$CHCl_3$ as eluent. No unchanged artemisinin was recovered; however, 3 products, **2** (4%), **3** (12%), and **4** (10%), were isolated and characterized. A substantial amount of colored material which stayed at the origin during chromatography was presumably polymeric.

Compound **2** is an oil which is homogeneous by TLC (silica gel, $CHCl_3$, R_f 0.46). CIMS gave the molecular weight of the compound to be 236 which indicates that **2** is formed by elimination of one molecule of formic acid from **1**. IR shows a five-membered lactone carbonyl (1785 cm^{-1}) and an enol ether double bond (1695 cm^{-1}). ^1H NMR exhibits a poorly resolved doublet at δ 4.66, indicating the presence of a β C-H of an enol ether, and a multiplet at 3.34 for the α-proton of the lactone carbonyl. The chemical shift and splitting pattern of the two methyl group resonances at δ 0.93 (d, J = 4.5 Hz) and 1.14 (d, J = 6.5 Hz) suggest that minimum structural changes in the carbons corresponding to C-6 (δ 0.99) and C-9 (δ 1.12) of artemisinin (**1**) occurred in **2**. However, the methyl group corresponding to C-3 CH_3 (δ 1.44) of compound **1** shifted δ 0.25 downfield (δ 1.68, d, J = 1.5 Hz) in compound **2** and long



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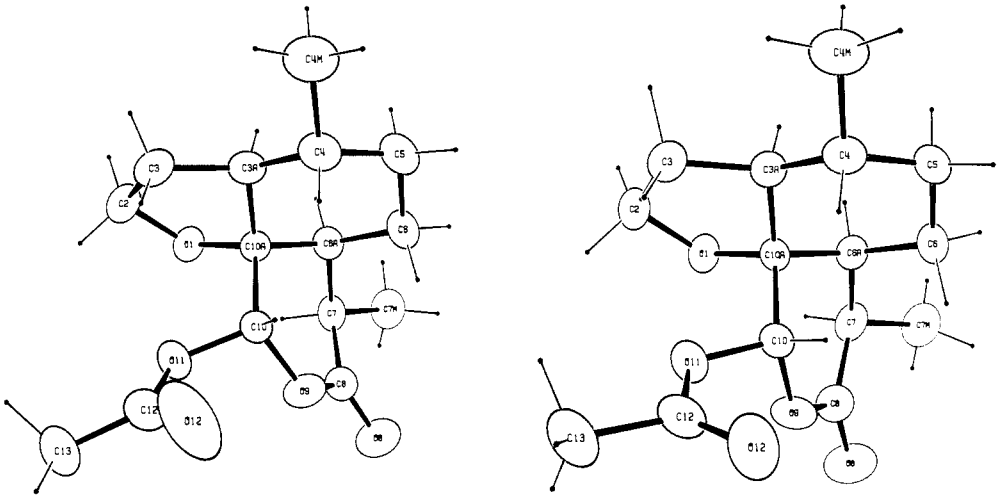

Figure 1. Crystal conformations of the two independent molecules of compound **3** (not a stereo diagram).

range coupled with a single proton, suggesting chemical changes occurred at C-3. ^{13}C NMR indicated the loss of one carbon atom from the parent compound **1**, and confirmed the existence of a lactone carbonyl (δ 179.31) and a trisubstituted enol ether double bond (δ 146.81 (s) and 97.51 (d)). The carbon atoms corresponding to δ 104.99 (s) and 146.81 (s) are fully substituted. These data led to the assignment of structure **2**, which, in comparison with the parent compound **1** with its seven asymmetric carbon centers, has only five chiral centers. Since the reaction did not involve the asymmetric carbons in **2** corresponding to C-6 and C-9 of artemisinin (**1**), their epimerization would not be aniticipated. However, epimerization at the carbon corresponding to C-5a, C-8a, and C-12a of **1** is possible during the formation of **2** (Scheme I). Nevertheless, based on the steric consideration during its formation, the most favorable conformation of cyclohexanone intermediate **7** requires that both bulky substituents at the 2 and 6 positions assume equitorial positions. Ring cyclization of **7** gives **8** with both protons at C-4a and C-8 in the α and the hydroxyl group in the β-configuration. Lactone formation of **8** gives the cis lactone **2** with the lactone oxygen atom in the β-configuration.

CIMS data indicate that **3** has the same molecular weight (282) as artemisinin. Its IR spectrum shows a strong absorption at 1760 cm^{-1}, suggesting a six-membered lactone or an ester. ^{13}C NMR confirms that the molecule contains 15 carbon atoms, including two ester carbonyls (δ 168.43 and 171.62), two carbons attached to one oxygen (δ 69.23 and 79.36), and one carbon linked to two oxygens (δ 93.02). Off-resonance studies indicates that δ 69.23, 79.36, and 93.02 carbons are secondary, fully substituted, and tertiary carbons, respectively. The ^1H NMR spectrum exhibits a proton resonance at δ 6.64 (s) which is δ 0.79 downfield from the H-12 of artemisinin (**1**), two multiplet protons (δ 4.22 and 3.94) characteristic of both the α protons of a tetrahydrofuran ring, and a multiplet (δ 3.18) corresponding to the H-9 of artemisinin. Three methyl groups at δ 2.16 (s), 1.21 (d, J = 7.2 Hz), and 0.99 (d, J = 5.4 Hz) again suggest that no change occurred at the carbons corresponding to C-6 and C-9 or their adjacent carbons of compound **1**. However, the methyl group at δ 2.16 in compound **3** is shifted downfield from the corresponding C-3 $-CH_3$ of artemisinin ($\Delta\delta$ = 0.72). These data suggest the existence of a tetrahydrofuran ring and a tertiary carbon linked to two ester functions. This led to the structure assignment of the rearrangement product as **3** in which the configuration of carbon atoms that correspond to C-5a, C-6, C-8a, C-9, C-12, and C-12a of artemisinin remains unchanged. Although IR absorption at 1760 cm^{-1} may appear to be off range for acetoxy and six-membered lactone carbonyls in compound **3**, mutual inductive effects of these two functions which are separated by one carbon caused the shift of their absorptions to higher wave numbers, an effect which has been documented.[9,10] The structural assignment of **3** is further confirmed by the X-ray crystallographic data shown in Figure 1.

The asymmetric unit contains two independent molecules. The final molecular dimensions are available as supplementary data. No chemical equivalent bond lengths differ by more than 3 estimated standard deviations and the average difference is 1.66 estimated standard deviations. Differences among bond angles are a little greater, but these are more susceptible to changes by intermolecular forces. While there are no significantly short intermolecular contacts, the conformations of the flexible parts of the two independent molecules are not identical and it is not possible to superimpose one molecule on the other by a local rotation (some atoms are as much as 0.5 Å apart in the least squares best results). Space group $A2$ is not unambiguously determined but the different conformations support the inference from the R factor that the space group chosen is indeed correct. It should also be noted that the configurations of the two independent molecules are the same and not opposite as they would be if the crystals were racemic. The absolute configuration of the molecule was determined by Engel's method[11] and the results indicate the correctness of the configuration as depicted in Figure 1 at the 0.0001 probability level. The statistic tested has the value of 2.2271 and the test level, calculated from $\chi^2_{21,0.0001}$, is 1.7891. The actual assignments of the chiral atoms are C-3a, S; C-4, R; C-6a, S; C-7, R; C-10, S; C-10a, R and are the same in both independent molecules.

CIMS data indicate that compound **4**, like **3**, is a rearrangement product of artemisinin with identical molecular weight. IR shows hydroxyl (3505 cm^{-1}) and six-membered lactone (1730 cm^{-1}) functions. Comparison of the ^{13}C NMR spectrum of compound **4** with that of **1** indicates the major difference is that one of the methylene carbons in **1** is linked to an oxygen atom in **4** (δ 69.02). This difference is also reflected in the ^1H NMR spectrum which exhibits

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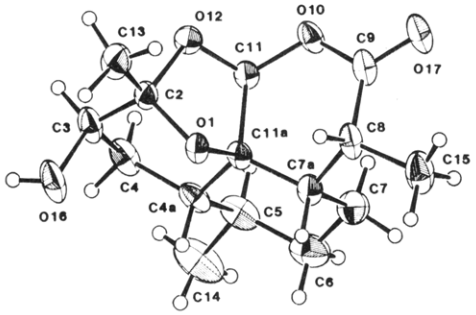

Figure 2. ORTEP drawing of compound **4** showing 25% probability ellipsoids.

an exchangeable singlet at δ 1.85 and a broad doublet at δ 3.63 (J = 8 Hz) for compound **4**, not observed in the spectrum of compound **1**. The broad doublet at δ 3.63 collapses into broad singlet with a half-width (W_H) equal to 7.5 Hz after D_2O exchange. Protons corresponding to H-12 (s, 1 H, δ 5.63), H-9 (m, 1 H, δ 3.22), C-6 $-CH_3$ (d, 3 H, J = 7.2 Hz, δ 1.20), C-9 $-CH_3$ (d, 3 H, J = 5.4 Hz, δ 0.94) and C-3 $-CH_3$ (s, 3 H, δ 1.57) of compound **1** are virtually unchanged in product **4**. The observation of coupling between hydroxyl and its adjacent C-H ruled out **5** or **9** as the possible structure of **4** and substantiates the structure assigned. Furthermore, the small W_H of the proton signal at δ 3.63 suggested that C-4 H is in an equatorial position[12] and thus unambiguously established the OH at C-4 to be in α-configuration. The structural assignment of **4** is further confirmed by X-ray crystallographic data as shown in Figure 2. Compound **4** forms four rings about central tertiary carbon (C-11a): ring A, a tetrahydropyran ring with an ether bridge from C-2 to C-11a, ring B (C11a–C4a–C5–C6–C7–C7a), ring C, (C11a–C11–010–C9–C8–C7a), and ring D, (C11a–01–C2–012–C11). Rings A and B are chair shaped whereas in ring C, C7a deviates by –0.66 Å from the least-squares plane through the remaining atoms whose maximum deviation from the plane is 0.08 Å. Bond distances and angles are available as supplementary data. The C–O single bond distances range from 1.329 (6) Å to 1.486 (7) Å and average 1.414 Å, somewhat less than the average value for saturated heterocyclic C–O single bonds of 1.426 (5) Å.[13] The packing is influenced by hydrogen bonding. The carboxy oxygen, 0(17), is hydrogen bonded to hydroxy H(16)–O(16) of a symmetry-related molecule (x, y, z – 1.0). The H-(16)′—O(17) distance is 2.08 (6) Å, the O(16)′—O(17) distance is 2.83 (2) Å, and the O(16)′–H(16)′—O(17) angle is 168.3 (4.8)°. An additional intermolecular approach less than the van der Waals separation is O(1)—H(11)′ (1.0 + x, y, z) of 2.45 (2) Å.

Interestingly, a compound with the structure of **4** is reported to be a constituent of *A. annua*;[14] however, a different melting point is given (172–173 °C), although similar ^{1}H NMR (except C-4H was reported as singlet rather than doublet) and EIMS data were reported. No ^{13}C or X-ray data are given to substantiate the structure assignment.[15]

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(15) We have been informed by Dr. A. Brossi that reinspection of the ^{1}H NMR and ^{13}C NMR spectra of an alcohol, mp 191–192 °C, derived from artemisinin and assigned a tetrahydrofuran-containing structure **9** (*Heterocycles* **1985**, *23*, 881), now suggests that the compound is more likely an ether analog of artemisinin with a hydroxy group at C-3 and is possibly identical with or closely related to our compound **4**.

A proposed mechanism that accounts for the formation of **2**, **3**, and **4**, involves the homolytic cleavage of the epidioxide bond of **1** to form the free radical **6**, as shown in Scheme I. The free radical **6** decomposes to generate anhydride **7** which undergoes cyclization to **8**. The intermediate **8** further cyclizes with the elimination of formic acid to yield **2**. The free radical intermediate **6** can also lead to the formation of an epoxide **5** which rearranges to give a stable alcohol **4** and an unstable hemiketal **9**. The latter rearranges further to give the isolated compound, **3**, possibly also by a radical mechanism.

Experimental Section

All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra of solid samples were obtained in KBr disks on a Perkin-Elmer Model 283 spectrophotometer. NMR spectra were run on a JEOL-FX-90Q spectrometer using Me_4Si as an internal standard and $CDCl_3$ as solvent. Mass spectra were determined on a Nermag R10-10 spectrometer integrated with an INCOS data system and operated in the CI mode using CH_4 as the reagent gas.

Thermal Decomposition of Artemisinin (1): Artemisinin[8] (1 g, 3.5 mmol) was placed in a 50-ml round bottom flask and was heated with stirring in a silicone-oil bath preheated at 190 °C. A vigorous reaction took place within 5 min and the heating was stopped after 10 min. The reaction mixture was allowed to cool to room temperature, and separation was carried out on a silica gel column using 7.5% EtOAc/$CHCl_3$ as eluent to give three major products, **2**, **3**, and **4**.

Compound **2** was rechromatographed on a silica gel column using $CHCl_3$ as eluent to give 40 mg (4%) of colorless oil. It gave a single spot on silica gel TLC; R_f 0.46 ($CHCl_3$) and 0.61 (EtOAc/petroleum ether, 1:10, v/v). $[\alpha]^{20}_D$ +6.5 (c 0.123, $CHCl_3$); CIMS (CH_4) m/z 237 (M + 1), 219, 209, 191, 179, and 166; IR (neat) 1785 (C=O) and 1695 (C=C—O) cm^{-1}; ^{1}H NMR δ 0.93 (d, J = 4.5 Hz, 3 H), 1.14 (d, J = 6.5 Hz, 3H), 1.68 (d, J = 1.5 Hz, 3H), 3.34 (m, 1 H) and 4.66 (b.d, 1 H); ^{13}C NMR δ 8.77, 18.96, 19.50, 21.61, 25.08, 32.29, 32.61, 38.95, 43.12, 43.73, 97.57, 104.99, 146.81, and 179.31.

Compound **3** crystallized from hexane as colorless prisms: mp 91–92 °C (120 mg, 12%); $[\alpha]^{20}_D$ +109.2 (c 0.109, $CHCl_3$); CIMS (CH_4), m/z 283 (M + 1), 223, 195, and 179; IR 1760 cm^{-1} (C=O), ^{1}H NMR δ 0.99 (d, J = 5.4 Hz, 3H), 1.21 (d, J = 7.2 Hz, 3 H), 2.16 (s, 3 H), 3.18 (m, 1 H), 3.94 (m, 1 H), 4.22 (m, 1 H), and 6.64 (s, 1 H); ^{13}C NMR δ 12.51, 20.37, 21.18, 24.27, 27.68, 30.84, 34.62, 34.98, 46.64, 54.84, 69.23, 79.36, 93.02, 168.43, and 171.62.

Compound **4** was recrystallized from EtOAc–petroleum ether as colorless needles, mp 190–192 °C (100 mg, 10%); $[\alpha]^{20}_D$ –131.1 (c 0.119, $CHCl_3$); CIMS, m/z 283 (M + 1), 265, 247, 237, and 219; IR 3505 (OH) and 1730 (C=O) cm^{-1}; ^{1}H NMR δ 0.94 (d, J = 5.4 Hz, 3H), 1.20 (d, J = 7.2 Hz, 3H), 1.57 (s, 3 H) 1.85 (s, 1 H, exchangeable with D_2O), 3.22 (m, 1 H), 3.63 (d, J = 7.2 Hz, 1 H), and 5.63 (s, 1 H); ^{13}C NMR δ 12.57, 18.42, 20.53, 23.51, 30.34, 32.72, 33.43, 35.16, 40.57, 42.09, 69.02, 82.94, 98.79, 108.93, and 171.46.

X-ray Crystallographic Data of Compound 3: An 0.2 mm cube was cut and sealed in a sphere of epoxy resin to avoid any possible loss of solvent during data collection. Preliminary X-ray investigation indicated a primitive cell with dimensions a = 8.136 (2) Å, b = 12.635 (4) Å, c = 15.145 (4) Å, α = 98.32 (2)°, β = 105.51 (2)°, and γ = 90.02 (2)°. The cell is metrically monoclinic and corresponds to an A cell. With 18 reflections, measured at $\pm\theta$ angles between 20 and 30°, least-squares refinement produced a cell with monoclinic dimensions a = 12.626 (1) Å, b = 8.142 (1) Å, c = 29.177 (3) Å, β = 98.65 (1)°, V = 2965.30 Å^3 (assume $\lambda_{CuK\alpha}$ = 1.5418 Å). The diffraction symmetry was truly monoclinic. Since the compound is optically active, the most likely space group is $A2$. However, with a molecular formula of $C_{15}H_{22}O_5$ (mol wt 282.34), there would need to be eight molecules in the unit cell to give the reasonable density of 1.265 and the asymmetric unit would be two molecules.

The X-ray intensity data were collected with an Enraf-Nonius CAD-4 diffractometer using Cu Kα X-radiation. With the above assumed content and space group, the phase problem was solved with MITHRIL.[16] The distribution of intensities was acentric and

all heavy atoms of both molecules were visible in the E map. Despite this promising result, attempts at solution were made in space groups $A2/m$ and Am but without success. The structure was refined by standard method using the program of XRAY72[17] (isotropic followed by anisotropic refinement of heavy atoms, finding H atoms in a difference map and finally refinement of all atoms with isotropic H thermal parameters). It proved necessary to carry out the refinement by alternately holding the parameters of one molecule constant and refining those of the other. The origin specification involves all the y parameters of one molecule and estimated standard deviations are given for all parameters. With 3228 observations (2273 with $I > \sigma(I)$) and a maximum $(\sin\theta)/\lambda$ of 0.6240 Å^{-1}, the final conventional R factor was 4.0%. The final atomic parameters and molecular dimensions are available as supplemental data, and the observed and calculated structure factors are available from J.V.S.

X-ray Crystallographic Data of Compound 4: $C_{15}H_{22}O_5$, mol wt = 282.34, $F(000)$ = 304, monoclinic $P2_1$, a = 5.465 (1), b = 13.752 (3), c = 9.831 (2) Å, and β = 101.71 (2). The unit cell volume is 723.4 (2) Å^3, Z = 2, and the calculated density is ρ_{calcd} = 1.296 mg mm^{-3}. A clear 0.21 mm × 0.07 mm × 0.08 mm crystal was used for data collection. The data were collected on a Nicolet R3m automated diffractometer with an incident-beam monochromator, λ = 1.54178 Å (Cu Kα), at T = 295 K. Lattice parameters were determined from 25 centered reflections between $16 \leq 2\theta \leq 55°$. The data collection range was $-6 \leq h \leq 3$, $0 \leq k \leq 15$, and $-10 \leq l \leq 10$ with $(\sin\theta)/\lambda_{max}$ = 0.56 Å^{-1}. Three standards were monitored every 60 reflections and exhibited a random variation of 3.4% over the data collection. A total of 1802 reflections were measured in the $\theta/2\theta$ mode with a scan width of 2.4°; scan rate was a function of count rate (4°/min minimum, 30°/min maximum). There were 1126 unique reflections, R_{int} = 0.038 from merging equivalent reflections, 966 observed with $F_o > 3\sigma(F_o)$. Lorentz and polarization corrections were applied, but no absorption correction was made; μ = 0.76 mm^{-1}.

The structure was solved by direct methods[18] with use of partial structure recycling.[19] The least-squares refinement program used the program SHELXTL.[20] In the block-cascade least squares the function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = 1/\sigma^2(|F_o| + g(F_o^2))$. The term $g(F_o^2)$ is included to account for random instrumental error (in the work g is estimated to be 0.0004). There were 194 parameters refined, including the atom coordinates and the anisotropic temperature factors for all non-H atoms. The y coordinate of O(1) was fixed to define the origin. Hydrogen atoms were fixed at ideal locations, and their isotropic temperature factors were fixed at 1.2 times the equivalent isotropic thermal parameters of the atom to which they were bonded. The coordinates and isotropic thermal parameter for H(16) were refined. The final residuals were R = 0.065 and R_w = 0.067 with an error in an observation of unit weight of S = 1.77 Å. Refinement of the other enantiomer gave residuals of R = 0.066 and R_w = 0.069 and S = 1.83, but the diffraction data were not accurate enough to determine the absolute configuration. The largest shift to error in the final cycle was 0.24, and the final difference Fourier excursions were −0.32 and 0.27 e Å^{-3}. Atomic scattering factors are from ref 21.

Supplementary Material Available: Tables of dimensions and coordinates for compounds **3** and **4** and ^{1}H and ^{13}C NMR spectra of compounds **2**, **3**, and **4** (32 pages). Ordering information is given on any current masthead page.

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The Design of Resolving Agents. Chiral Cyclic Phosphoric Acids

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A systematic investigation has been started with the twofold purpose of synthesizing efficient resolving agents and of gaining an insight into the factors that contribute to successful resolutions. We report on the synthesis, resolution, and application of a number of chiral cyclic phosphoric acids. Among these acids, 4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide (**7A**) is an efficient resolving agent, being useful for the resolution of amines and amino acids. Acid chloride **20** is a useful reagent for the determination of the ee of chiral amines. The absolute configuration of (−)-**7A** was determined through an X-ray structure determination of its salt with (−)-(*p*-hydroxyphenyl)glycine.

The rising demand for optically pure compounds has focused increasing attention on asymmetric synthesis. In spite of the successes achieved in this field, the classical resolution—through formation and separation of diastereoisomeric salts—remains the mainstay for the production of pure enantiomers, especially for their production on a multigram scale. To meet the demand for optically pure compounds the availability of a large and diverse group of resolving agents is necessary. Although in principle nature provides us with a virtually unlimited variety of resolving agents, the actual number of useful and readily available agents is barely a dozen.[1] The last decades have therefore seen the birth of synthetic resolving agents (where both enantiomers are usually available), which may give successful resolutions where natural resolving agents fail.[1] However, most of these synthetic resolving agents are semisynthetic (i.e. derived from natural, optically pure materials), and to our knowledge no systematic research toward the development of new resolving agents from *achiral* starting materials has been performed. In this paper we present the first results of our search for new

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