Inversion of Sign of Rotation during Resolution/Racemization. Small crystals of (D-ACL)$_3$NiCl$_2$·EtOH (100% ee) were prepared by precipitation from a concentrated methanol solution with ethanol. The crystals had an average size of 3.5 μm as determined with a Coulter counter. Large crystals of (L-ACL)$_3$NiCl$_2$·EtOH (97% ee) were the product of a long semicontinuous resolution/racemization run and had an average size of 27 μm.

A solution of DL-ACL (1.65 g, 12.9 mmol) in ethanol containing 2.86 mmol of $NiCl_2$ and 0.43 mmol of NaOEt in a 9.5-mL volume was heated to reflux. A mixture of 273 mg of the L-ACL complex (large crystals) and 226 mg of the D-ACL complex (small crystals) was added as seed crystals, $[\alpha]^{25}_D$ −1.8°. Reflux was continued for 22 h, during which time some of the solvent was allowed to distill off. The crystals were filtered, washed with ethanol, and dried in vacuo at 80 °C to give 1.291 g (49% conversion) of (ACL)$_3$NiCl$_2$·EtOH, $[\alpha]^{25}_D$ +13.3 (c 4, 1 N HCl). This represents a gain of 788 mg of (D-ACL)$_3$NiCl$_2$·EtOH and 4 mg of (L-ACL)$_3$NiCl$_2$·EtOH.

Ligand Exchange about Nickel. A solution of (D-ACL)$_3$NiCl$_2$·EtOH (72 mg, 0.13 mmol) in 10 mL of methanol, α_D −0.41°, was mixed at room temperature with a solution of L-ACL (50 mg, 0.387 mmol) in 10 mL of methanol, α_D −0.165°. The optical rotation was measured as soon as possible (~10 s from mixing) and found to be α_D −0.03° and remained constant at this value. Thus racemization (exchange) about the metal is very fast on the time scale of the resolution/racemization experiments.

Acknowledgment. We thank W. J. Lukasavage for technical assistance in the course of this work and Professor Ernest Eliel for helpful discussions and suggestions concerning the manuscript.

Registry No. 1, 17929-90-7; (ACL)$_3$NiCl$_2$, 31797-34-9; (ACL)$_2$NiCl$_2$, 29872-01-3; L-ACL, 21568-87-6; D-ACL·HCl, 26081-03-8; L-ACL·HCl, 26081-07-2; L-ACL·L-PCA, 39178-99-9; methyl L-lysinate dihydrochloride, 26348-70-9; L-lysine hydrochloride, 10098-89-2; L-PCA, 98-79-3.

Phosphonate Reagents for the Synthesis of Enol Ethers and One-Carbon Homologation to Aldehydes[1,2]

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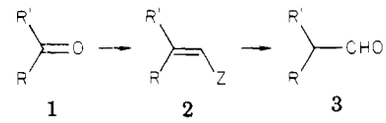
Phosphonate reagents **7a,b,d** were developed for the preparation of enol ethers **2** (Z = OR) from carbonyl compounds **1**. The phosphonates **7** were smoothly deprotonated with lithium diisopropylamide and these lithiated species were reacted with **1** to give intermediates **8**. The enol ether **2** (Z = OR) was obtained from **8** directly by heating at reflux or in two steps by quenching with water to give **9**, followed by reaction of **9** with potassium *tert*-butoxide. For enolizable **1** high yields of **9** could be obtained by addition of **1** to lithiated **7** at −100 °C. Reagents **7a** and **7b** afforded THP enol ethers **2** (Z = OTHP), which were convertable to homologated aldehydes **3** with mild acid hydrolysis. Reagent **7c** gave high yields of 1,2-adducts **9**, but these were not efficiently transformed to **2** (Z = OSi-*t*-BuMe$_2$) by reaction with potassium *tert*-butoxide: the adduct from **7c** and benzophenone gave **10** in 18% yield.

An ample measure of the "violent development" of synthetic methods in recent years has been directed at producing reagents with reactivity umpolung.[4] Several methods involving reactivity umpolung have been developed for one-carbon homologation of carbonyl compounds **1** to aldehydes **3**. Several of these methods have proceeded



1 **2** **3**

through intermediates **2** in which Z was an oxygen, a nitrogen, or a sulfur radical (OR, NR$_2$, SR).[5]

In connection with a synthesis of the alkaloid ajmaline we required a reagent that could give a one-carbon homologation of a ketone to an aldehyde. We chose to achieve this transformation by proceeding through an enol ether **2** (Z = OR). One of the reports of enol ether synthesis with triphenylphosphorane ylides pointed to the attractive possibility of incorporating a tetrahydropyranyl group in **2** (Z = OTHP),[6] thereby allowing for very mild acid hydrolysis in converting **2** to **3**. Unfortunately, the alkoxymethyltriphenylphosphorane ylides used to make enol ethers **2** were known to be unstable[7] and to give low yields with enolizable substrates.[8,9] A diphenylphosphine oxide reagent was known to give satisfactory yields with enolizable substrates,[10] but this reagent gave methyl enol ethers (**2**, R = OCH$_3$) which were not, in our opinion, subject to hydrolysis under suitably mild conditions. A phosphonamide reagent for preparing enol ethers was also deemed unattractive since it gave ethyl enol ethers and also since it afforded only modest yields (42–47%) with enolizable substrates.[11]

In principle it seemed that a phosphonate reagent could be a reasonable means for achieving the transformation of **1** to **2**, so reasonable in fact that the literature contained two accounts of such attempts. It was reported that phosphonate **4a** was recovered unchanged from an attempted reaction with sodium hydride and benzaldehyde.[12] Lavielle had shown that phosphonate **4b** gave less than

(1) Contribution No. 538 from the Institute of Organic Chemistry.
(2) For a preliminary account of this work see: Kluge, A. F. *Tetrahedron Lett.* **1978**, 3629.
(3) Syntex Postdoctoral Fellow, 1977–1979.
(4) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.
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(9) Ferwanah, A.; Pressler, W.; Reichardt, C. *Tetrahedron Lett.* **1973**, 3979.
(10) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Chem. Commun.* **1977**, 314.
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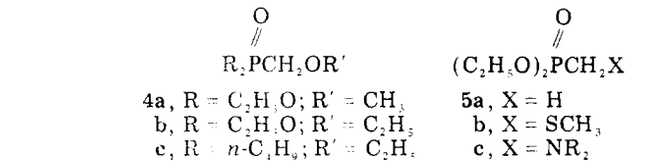


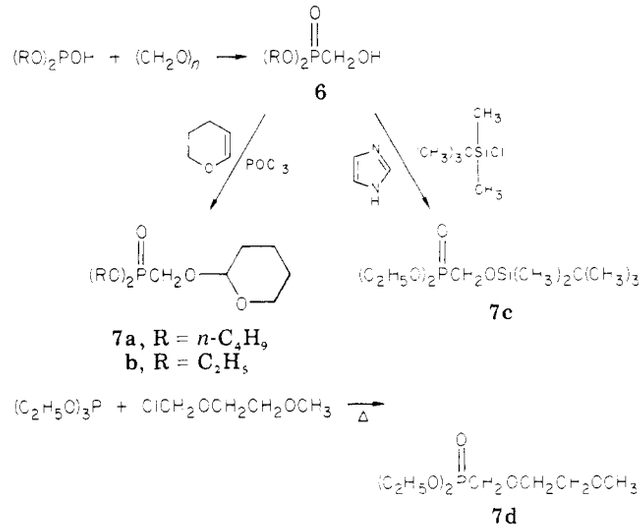
a 10% yield of an enol ether upon reaction with benzaldehyde and potassium *tert*-butoxide;[11] furthermore, it was found that attempted metalation of **4b** with *n*-butyllithium gave rise instead to a substitution reaction on phosphorus to afford a 30% yield of **4c**.[11,13] This last result was in marked contrast to the facile metalation of phosphonates **5a–c** with *n*-butyllithium.[14]

Despite the inauspicious augeries associated with the two previous reports of phosphonate reagents for enol ether synthesis, we decided to investigate these species further (Scheme I). The hydroxyl-protected species **7a–c** were obtained from the readily available (hydroxymethyl)-phosphonates **6**.[15] Compound **7d** was made by Arbusov reaction of MEM chloride[16] and triethyl phosphite. We were unable to convert **6** (R = *n*-C_4H_9) into either the MEM-protected ether using (MEM)$NEt_3^+Cl^-$[16] or into the methyl–thiomethyl-protected ether using dimethyl sulfoxide–acetic anhydride.[17]

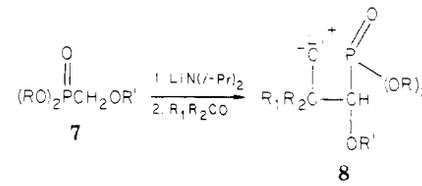
The Wittig–Horner reaction with reagents **7** proved to be highly satisfactory as a synthetic method (Table I). The reaction was initiated by deprotonation of **7** using lithium diisopropylamide in THF–hexane at −78 °C. Attempted metalation of **7d** with *n*-butyllithium afforded as yet uncharacterized material that was presumed to be derived from substitution on phosphorus in the manner reported by Lavielle.[11,13] The lithiated species **7** gave low yields of 1,2-addition products with enolizable substrates at −78 °C (entries for cyclopentanone and acetophenone); however, when the reaction temperature was lowered to −100 °C, yields of 90% and better were obtained from these otherwise troublesome substrates. The α,β-unsaturated substrates cinnamaldehyde and chalcone afforded acceptable yields of products attributable to 1,2-addition. Problems were encountered with steric hinderance as shown by the low yields obtained with ketone i and with camphor.

The Wittig-Horner synthesis of enol ethers as shown in Table I was performed either as a one-pot or as a two-step operation (Scheme II). In the one-pot synthesis the lithiated reagent **7** was condensed with an aldehyde or ketone at −78 °C or −100 °C, and then the reaction mixture was warmed to reflux and was held at that temperature until TLC analysis indicated that the initially formed 1,2-adduct **8** had undergone elimination to form enol ether **2**. The reflux time varied according to the nature of the substrate carbonyl compound: the intermediates derived from chalcone and benzophenone required between 2 and 4 h at reflux; the adduct from acetophenone required between 10 and 16 h; the adduct from cyclohexanone required approximately 48 h; the adduct from cyclopentanone had undergone only 40% reaction after 72 h at reflux. These substituent effects on the time course for the transformation of **8** to **2** were wholly in accord with the requirement for stabilization of positive charge buildup

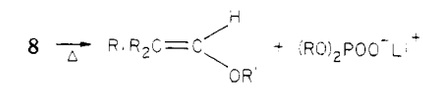
Scheme I. Preparation of (Alkoxymethyl)phosphonate Esters



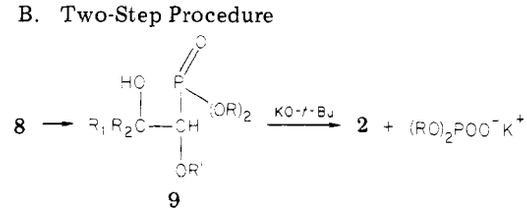
Scheme II. Wittig-Horner Olefination with (Alkoxymethyl)phosphonate Esters



A. One-Pot Procedure



B. Two-Step Procedure



β to the phosphorus moiety in the transition state for the four-centered Wittig olefination. The concomitant buildup of negative charge α to the phosphorus moiety in the olefination transition state was stabilized by the inductive effect of the oxygen substituent.[18] Because of the prolonged reaction times required in certain cases we found it convenient to perform the reaction in two steps comprised in turn by isolation of the 1,2-adduct **9** followed by reaction with potassium *tert*-butoxide. The potassium *tert*-butoxide functioned to exchange the lithium cation in **8** with potassium, thereby giving a more ionic species that required less activation energy to achieve the transition state for four-centered elimination than did the lithio species **8**. The literature indicated that a similar situation applied with the two-step, phosphine oxide based synthesis of enol ethers wherein the second step involved reaction of the isolated 1,2-adduct with sodium hydride to achieve olefination.[10] Unfortunately, we were not able to reduce the reflux time of the one-pot procedure by the addition

(13) Sturtz, G.; Lavielle, G.; Normant, H. *Chem. Ztg.* **1972**, *96*, 503.
(14) (a) Corey, E. J.; Kwaitkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654. (b) Corey, E. J.; Shulman, J. I. *J. Org. Chem.* **1970**, *35*, 777. (c) Martin, S. F.; Gomper, R. *J. Org. Chem.* **1974**, *39*, 2814.
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(16) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.
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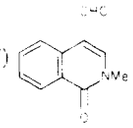
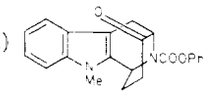
(18) The reflux times required for elimination of the 1,2-adducts appear to be on the order of those required for a methylthio substituent α to phosphorus: see ref 14b.

Table I. Conversion of R_1R_2CO to 1,2-Adducts (9), Enol Ethers (2), and R_1R_2CO

substrate	reagent	yield[a] of 9, %	yield[b,c] of 2, %	yield for hydrolysis of 2, %
(a) benzophenone	7a	92	67 (85)	89
	7c	91	(29)	82
	7d	86	73 (90)	
(b) acetophenone	7a	60, 95[d]	83[e] (65)[e]	90
	7d	66	56	72
(c) cyclohexanone	7a	99[d]	84[e] (97)[e]	87
	7b		79[e]	
	7c	72		
	7d	83	61 (86)	80
(d) cyclopentanone	7a	36, 90[d]	79[e] (36)[e,f]	92
	7d	38		
(e) 2-naphthaldehyde	7d	80	48	50
(f) 	7a		79	75
(g) cinnamaldehyde	7a	99	79	
(h) chalcone	7a		(55)	
(i) 	7a		37[e]	
(j) 	7a	12		

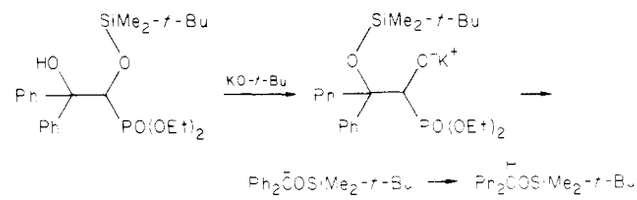
[a] Addition of substrate to lithiated 7 performed at −78 °C unless otherwise noted. [b] Yields refer to the two-step procedure whereby 9 is isolated and is then reacted with potassium *tert*-butoxide in THF. [c] Yield in parentheses refers to the one-pot procedure. [d] Yield at −100 °C. [e] Substrate added to lithiated 7 at −100 °C. [f] After 72 h at reflux only 40% of 1,2-adduct had eliminated.

of potassium *tert*-butoxide to a solution of the adduct 8 derived from cyclohexanone.

Comparison of yields of enol ether formation from reagents **7a,b,d** with other literature reports shows some preparative advantage with our reagents. These reagents give substantially higher yields of enol ethers with cyclopentanone and cyclohexanone than does methoxymethylenetriphenylphosphorane.[7] In the case of cyclohexanone, **7a** also gives a better yield of enol ether **2** than either the diphenylphosphine oxide reagent of Warren[10] or the phosphonamide reagent of Lavielle.[11] If one compares the yields of aldehydes obtained by this method with the yields reports from the α-chloro-α-(trimethylsilyl) carbanion technique of Magnus,[19] it appears that there are not marked differences between the two methods.

In a search for an oxygen protecting group other than THP, the *tert*-butyldimethylsilyl protecting group was investigated. The silyloxy reagent **7c** was not effective in the Wittig–Horner reaction. Good yields of 1,2-addition product **9** were obtained from both benzophenone and cyclohexanone; however, the subsequent reaction of these adducts with potassium *tert*-butoxide gave complicated mixtures. In the case of the benzophenone-derived material there was obtained 18% of the silylated benzhydrol **10**, a result that indicated that transsilylation might have been the culprit behind the low yields (Scheme III). An attempt at performing the reaction as a one-pot procedure gave only a 29% yield of the silylated enol ether derived from benzophenone.

Scheme III



10

Experimental Section

NMR spectra were determined with a Varian A-60A or a Varian HA-100 spectrometer using solutions of ca. 10% (v/v) of the compound in deuteriochloroform with 1% tetramethylsilane as an internal standard. Mass spectra were obtained with an Atlaswerke CH-4 instrument. Elemental analyses were performed by Syntex Analytical Department and by A. Bernhardt, Mülheim-Ruhr.

Dibutyl [(2-Tetrahydropyranyloxy)methyl]phosphonate (7a). A mixture of 155.2 g (0.8 mol) of dibutyl phosphite, 24 g (0.8 mol) of paraformaldehyde, and 8 g of triethylamine was heated at 110 °C for 6 h. Volatile material was removed by using an Aldrich Kugelrohr apparatus (100 °C, 5 mm). This procedure gave 173 g of crude dibutyl (hydroxymethyl)phosphonate. This material was mixed with 33 g (0.39 mol) of dihydropyran, 350 mL of diethyl ether, and 8 drops of phosphorus oxychloride in a flask that was fitted with a drying tube. After 15 min another 33 g of dihydropyran and 8 drops of phosphorus oxychloride were added. These additions were repeated three more times at 15-min intervals. After 2 h an additional 1 mL of phosphorus oxychloride was added. TLC analysis (Et_2O) showed the reaction was complete after 4 h. The mixture was diluted with 200 mL of diethyl ether, and the resulting mixture was shaken with 300 mL of 5% sodium bicarbonate solution. The organic layer was separated and was washed with 100 mL of saturated sodium chloride solution. After being separated and dried (Na_2SO_4), the organic layer was evaporated to give 204 g of crude product. This material was filtered through 350 g of silica gel 60 (70–230 mesh) with 80% diethyl ether–hexane. Distillation of this chromatographed material gave 155 g of **7a**: bp 138–140 °C (0.1 mm); NMR δ 0.95 (*t*, 6 H, *J* = 6.5 Hz), 1.1–2.0 (m, 14 H), 3.4–4.35 (m, 8 H), 4.72 (m, 1 H); mass spectrum (70 eV), *m/e* 307 (M − 1).

(19) Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1977**, *99*, 4536.

Anal. Calcd for $C_{14}H_{29}PO_5$: C, 54.53; H, 9.48; P, 10.05. Found: C, 54.72; H, 9.42; P, 10.27.

A sample of **7a** that was stored in a brown glass bottle at room temperature for 1 year showed considerable impurities by TLC analysis. This aged **7a** was not suitable for reaction with carbonyl compounds; however, full reactivity was restored by chromatographing this material on silica gel with 80% diethyl ether–hexane.

Diethyl [(2-Tetrahydropyranyloxy)methyl]phosphonate (7b). A mixture of 54.6 g (0.396 mol) of diethyl phosphite, 11.85 g (0.395 mol) of paraformaldehyde, and 3.91 g of triethylamine was heated for 6 h at 120 °C. Distillation with an Aldrich Kugelrohr apparatus (120 °C, 0.1 mm) gave 32.1 g (48%) of diethyl (hydroxymethyl)phosphonate. This was mixed with 16.4 g of dihydropyran and 100 mL diethyl ether, and 10 drops of phosphorus oxychloride was added. After 30 min another 8 g of dihydropyran and 5 drops of phosphorus oxychloride were added. TLC analysis (EtOAc) showed the reaction to be complete after 3.5 h. The mixture was diluted with 100 mL of diethyl ether, and the resulting mixture was washed in turn with 150 mL of 5% sodium bicarbonate solution and 100 mL of saturated sodium chloride solution. After being separated and dried (Na_2SO_4), the organic layer was evaporated to give an oil. Distillation with an Aldrich Kugelrohr apparatus (105 °C, 0.1 mm) gave 39.4 g (ca. 82%) of **7b** of ca. 95% purity. This sample was suitable for use without further purification. Material of higher purity was obtained by chromatography on silica gel 60 (70–230 mesh) using ethyl acetate. The chromatographed material was distilled with a Kugelrohr apparatus (105 °C, 0.1 mm): NMR δ 1.35 (t, 6 H, J = 7 Hz), 1.4–1.9 (m, 6 H), 3.4–4.45 (m, 8 H), 4.7 (m, 1 H).

Anal. Calcd for $C_{10}H_{21}PO_5$: C, 47.61; H, 8.39. Found: C, 47.87; H, 8.1.

Diethyl [(*tert*-Butyldimethylsilyloxy)methyl]phosphonate (7c). A mixture of 16.8 g (0.1 mol) of diethyl (hydroxymethyl)phosphonate, 18.09 g (0.12 mol) of *tert*-butylchlorodimethylsilane, 17 g (0.25 mol) of imidazole, and 34 mL of DMF was stirred at 35 °C overnight. The mixture was poured into 250 mL of water, and this mixture was extracted thoroughly with diethyl ether. The organic layer was dried (Na_2SO_4) and evaporated to give 23.4 g of crude product. Distillation afforded 12.8 g (45%) of **7c**: bp 85 °C (0.1 mm); NMR δ 0.05 (s, 6 H), 0.83 (s, 9 H), 1.25 (t, 6 H, J = 7 Hz), 3.86 (d, 2 H, J = 8 Hz), 4.12 (m, 4 H); mass spectrum (70 eV), m/e 282 (M^+).

Anal. Calcd for $C_{13}H_{27}PSiO_4$: C, 46.78; H, 9.67; P, 10.97. Found: C, 46.72; H, 9.56; P, 10.87.

Diethyl [(2-Methoxyethoxy)methyl]phosphonate (7d). A mixture of 6.23 g (50 mmol) of MEM chloride[16] and 8.72 g (52.5 mmol) of triethyl phosphite was heated at 155 °C for 3 h in a round-bottom flask equipped with a magnetic stirrer and a reflux condenser. Distillation afforded 8.4 g (74%) of **7d**: bp 104–105 °C (0.8 mm); NMR δ 1.32 (t, 6 H, J = 7 Hz), 3.32 (s, 3 H), 3.45–3.8 (m, 4 H), 3.83 (d, 2 H, J = 8 Hz), 3.97–4.32 (m, 4 H).

Anal. Calcd for $C_8H_{11}PO_5$: C, 42.47; H, 8.47; P, 13.69. Found: C, 42.33; H, 8.44; P, 13.71.

General Procedures. To a 100-mL round-bottom flask equipped with a thermometer, a rubber septum, a Herschberg dropping funnel, a gas-inlet tube, and a magnetic stirrer were added 2.94 mL of diisopropylamine (21 mmol) and 30 mL of THF. The contents of the flask were maintained under a positive pressure of argon. The contents were cooled to ca. −78 °C with a methanol bath. A hexane solution of *n*-butyllithium (13.4 mL of 1.5 M solution) was added at once. The phosphonate **7** (20 mmol) was added over 5 min with a syringe. A solution of 18.7 mmol of ketone or aldehyde in 15 mL of THF was added dropwise over 15–30 min. For reactions at −100 °C the temperature of the methanol cooling bath was lowered by the addition of liquid nitrogen. After the addition of the carbonyl compound was complete, the reaction was taken through one of two alternate procedures.

Procedure A. The dropping funnel was replaced with a reflux condenser, and the cooling bath was replaced with a heating mantle. The mixture (under argon) was heated at reflux until TLC analysis indicated that the polar 1,2-adduct had been converted into the less polar **2**. The mixture was poured onto 150 mL of diethyl ether. This mixture was washed in turn with 50 mL of 20% citric acid, 50 mL of water, and 50 mL of 5% sodium bicarbonate solution. The organic layer was evaporated, and the residue was filtered through 50 g of silica gel 60 (70–230 mesh) with 20% diethyl ether–hexane. Evaporation of the filtrate afforded pure **2**.

Procedure B. The reaction mixture was poured onto 150 mL of diethyl ether, and the resulting mixture was washed in turn with 50 mL of citric acid, 50 mL of water, and 50 mL of 5% sodium bicarbonate solution. The organic phase was concentrated by evaporation, and the residue was chromatographed on 125 g of silica gel 60 (70–230 mesh) with an elution gradient of 50% diethyl ether–hexane to 75% diethyl ether–hexane. This procedure gave analytically pure 1,2-adduct **9**. The 1,2-adduct **9** was dissolved in THF (ca. 1 g/5 mL) and 2 equiv of potassium *tert*-butoxide were added with stirring. The resulting mixture was warmed on a steam bath for 5 min. The mixture was poured onto 150 mL of diethyl ether, and the resulting mixture was washed with two 50-mL portions of water. The organic phase was concentrated by evaporation, and the residue was filtered through silica gel 60 (70–230 mesh) (ca. 3 g/g of starting material **9**) with 40% diethyl ether–hexane. The filtrate was concentrated by evaporation to give the enol ether **2**.

Hydrolysis of Enol Ethers 2 to Aldehydes. (I) THP Enol Ethers. The enol ether **2** was dissolved in THF (ca. 10 mL/g of **2**) in a round-bottom flask equipped with a magnetic stirrer. The contents of the flask were maintained under argon. Water was added until the solution became turbid. The mixture was purged of oxygen by evacuation followed by recharging with argon. Sufficient concentrated hydrochloric acid was added to achieve a ca. 0.2 N solution of HCl. The mixture was stirred at room temperature from 2 to 8 h, and the course of the reaction was monitored periodically by TLC and GLC. After complete disappearance of **2** the mixture was poured onto excess 5% sodium bicarbonate solution, and the resulting mixture was extracted thoroughly with diethyl ether. After being dried over Na_2SO_4, the ether extract was evaporated to give a crude product. Further purification was obtained by filtration through silica gel 60 (70–230 mesh) with 20% diethyl ether–hexane. The yields in Table I are for pure, isolated compounds, except for those aldehydes that were derived from cyclopentanone and cyclohexanone, both of which were determined by GLC. All the aldehydes except that derived from aldehyde f were compared to authentic samples.

(II) 2-Methoxyethyl Enol Ethers. To a round-bottom flask equipped with a magnetic stirrer, reflux condenser, and gas-inlet tube were added the enol ether **2** and THF (ca. 10 mL/g of **2**). Water was added until the solution became turbid. The mixture was purged of oxygen by evacuation followed by recharging with argon. Sufficient 70% perchloric acid was added to make the solution 2% in perchloric acid. The mixture was heated in a 60 °C oil bath for ca. 6 h. The isolation procedure for the aldehyde was identical with that followed in I.

(III) Hydrolysis of 1,1-Diphenyl-2-(*tert*-butyldimethylsilyloxy)ethene (25). A mixture of 1.6 g of the silylated enol ether, 5 mL of THF, and 10 mL of 65% acetic acid was stirred under argon at room temperature for 18 h. The mixture was poured onto 100 mL of diethyl ether, and the resulting solution was washed with two 50-mL portions of 5% sodium bicarbonate solution. The organic phase was concentrated by evaporation, and the residue was filtered through 10 g of silica gel 60 (70–230 mesh) with 20% diethyl ether–hexane. Evaporation of the filtrate gave 0.83 g (82%) of diphenylacetaldehyde that was identical with an authentic sample by IR spectroscopy and by GLC.

(IV) Hydrolysis of 1-(2-Methyl-1-oxo-1,2-dihydro-4-isoquinolyl)-2-(2-tetrahydropyranyloxy)ethene (33). Argon was passed through a solution of 3.5 g (12.3 mmol) of **33**, 30 mL of THF, and 4 mL of 1 N HCl for 5 min. The mixture was stirred at room temperature for 8 h. The oily aldehyde product (1.86 g, 75%) was isolated according to the procedure in I. This aldehyde was reduced with sodium borohydride in ethanol to give 2-methyl-4-(2-hydroxyethyl)-1-isoquinolone (**37**): mp 173–175 °C; NMR δ 2.93 (t, 2 H, J = 6.5 Hz), 3.37 (br s, 1 H, OH), 3.49 (s, 3 H, CH_3), 3.88 (t, 2 H, J = 6.5 Hz), 7.02 (s, 1 H), 7.3–7.8 (m, 3 H), 8.32–8.5 (m, 1 H); mass spectrum (70 eV), m/e 203 (M^+).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.91; H, 6.52; N, 6.99.

Physical and Analytical Data for 1,2-Adducts 9. Dibutyl [1-(2-Tetrahydropyranyloxy)-2-hydroxy-2,2-diphenylethyl]phosphonate (11): oil; NMR δ 0.65–1.9 (m, 20 H), 2.8–4.2

(m, 6 H), 4.35–4.7 (m, 1 H), 5.01 (br s, 1 H) 5.5 and 5.6 (2 s, 1 H, OH), 7.05–8.1 (m, 10 H).

Anal. Calcd for $C_{27}H_{39}PO_6$: C, 66.1; H, 8.01. Found: C, 66.15; H, 8.12.

Diethyl [1-(*tert*-Butyldimethylsilyloxy)-2-hydroxy-2,2-diphenylethyl]phosphonate (12): mp 88–89 °C; NMR δ 0.05 (s, 6 H), 0.73 (s, 9 H), 0.92–1.43 (m, 6 H), 2.95–4.28 (m, 4 H), 4.58 (d, 1 H, J = 6.5 Hz), 5.5 (s, 1 H, OH), 7.1–8.1 (m, 10 H); mass spectrum (70 eV), m/e 447 (M – OH).

Anal. Calcd for $C_{24}H_{37}SiPO_5$: C, 62.04; H, 8.03; P, 6.67. Found: C, 62.37; H, 7.92; P, 6.4.

Diethyl [1-(2-Methoxyethoxy)-2-hydroxy-2,2-diphenylethyl]phosphonate (13): oil; NMR δ 1–1.25 (m, 6 H), 3.1 (s, 3 H), 3.15–4.05 (m, 8 H), 4.3 (d, 1 H, J = 8.5 Hz), 5.4 (s, 1 H, OH), 7–7.9 (m, 10 H); mass spectrum (70 eV), m/e 391 (M – OH).

Anal. Calcd for $C_{21}H_{29}PO_6$: C, 61.75; H, 7.16. Found: C, 61.8; H, 7.16.

Dibutyl [1-(2-Tetrahydropyranyloxy)-2-hydroxy-2-phenylpropyl]phosphonate (14): oil; NMR δ 0.7–1.85 (m, 17 H), 3.1–4.45 (m, 7 H), 4.86 (br s, 1 H), 5.1 (br s, 1 H, OH), 7.15–7.8 (m, 5 H).

Anal. Calcd for $C_{22}H_{37}PO_6$: C, 61.66; H, 8.7. Found: C, 61.27; H, 8.56.

Diethyl [1-(2-Methoxyethoxy)-2-hydroxy-2-phenylpropyl]phosphonate (15): oil; NMR δ 0.95–1.48 (m, 6 H), 1.69 (br s, 3 H), 3.28 and 3.32 (2 s, 3 H, CH_3O), 3.38–4.5 (m, 9 H), 4.7 (br s, 1 H, OH), 7.15–7.75 (m, 5 H); mass spectrum (70 eV), m/e 328 (M – H_2O).

Anal. Calcd for $C_{16}H_{27}PO_6$: C, 55.48; H, 7.86. Found: C, 55.2; H, 7.87.

Dibutyl [(2-Tetrahydropyranyloxy)(1-hydroxycyclohexyl)methyl]phosphonate (16): oil; NMR δ 0.75–2 (m, 30 H), 3.25–4.4 (m, 8 H), 4.7 (br s, 1 H); mass spectrum (70 eV), m/e 322 (M – THP).

Anal. Calcd for $C_{20}H_{34}PO_6$: C, 59.09; H, 9.67; P, 7.62. Found: C, 59.06; H, 9.68; P, 7.57.

Diethyl [(*tert*-Butyldimethylsilyloxy)(1-hydroxycyclohexyl)methyl]phosphonate (17): oil; NMR δ 0.05 (s, 6 H), 0.85 (s, 9 H), 1.1–1.8 (m, 16 H), 3.7 (d, 1 H, J = 5.5 Hz), 3.76 (s, 1 H, OH), 3.82–4.4 (m, 4 H); mass spectrum (70 eV), m/e 323 (M – C_4H_9).

Anal. Calcd for $C_{17}H_{37}SiPO_5$: C, 53.65; H, 9.8. Found: C, 53.32; H, 9.85.

Diethyl [(2-Methoxyethoxy)(1-hydroxycyclohexyl)methyl]phosphonate (18): oil; NMR δ 1.37 (t, 6 H, J = 7 Hz), 1.5–2 (m, 10 H), 3.4 (s, 3 H), 3.5–4.6 (m, 10 H).

Anal. Calcd for $C_{14}H_{29}PO_6$: C, 51.84; H, 9.01. Found: C, 51.92; H, 8.83.

Dibutyl [(2-Tetrahydropyranyloxy)(1-hydroxycyclopentyl)methyl]phosphonate (19): oil; NMR δ 0.75–2.3 (m, 28 H), 3.3–4.3 (m, 7 H), 4.8 (br s, 1 H).

Anal. Calcd for $C_{19}H_{37}PO_6$: C, 58.14; H, 9.5; P, 7.89. Found: C, 57.98; H, 9.34; P, 7.87.

Diethyl [(2-Methoxyethoxy)(1-hydroxycyclopentyl)methyl]phosphonate (20): oil; NMR δ 1.34 (t, 6 H, J = 7 Hz), 1.55–2 (m, 8 H), 3.37 (s, 3 H), 3.45–4.4 (m, 10 H).

Anal. Calcd for $C_{13}H_{27}PO_6$: C, 50.31; H, 8.77. Found: C, 50.33; H, 8.93.

Diethyl [1-(2-Methoxyethoxy)-2-hydroxy-2-(2-naphthyl)ethyl]phosphonate (21): oil; NMR δ 0.95–1.42 (m, 6 H), 3.11 and 3.24 (2 s, 3 H, OCH_3), 3.3–4.4 (m, 10 H), 4.95–5.3 (m, 1 H), 7.3–8 (m, 7 H); mass spectrum (70 eV), m/e 382 (M^+).

Anal. Calcd for $C_{19}H_{27}PO_6$: C, 59.68; H, 7.12. Found: C, 59.46; H, 7.15.

Dibutyl [1-(2-Tetrahydropyranyloxy)-2-hydroxy-4-phenylbut-3-enyl]phosphonate (22): oil; NMR δ 0.7–2 (m, 20 H), 3.3–5 (m, 10 H), 6.15–7.6 (m, 7 H); mass spectrum (70 eV), m/e 440 (M^+).

Anal. Calcd for $C_{23}H_{37}PO_6$: C, 62.71; H, 8.47; P, 7.03. Found: C, 62.8; H, 8.31; P, 7.12.

1,2-Adduct from 7a and Camphor (23): oil; NMR δ 0.75–2.3 (m, 36 H), 3.2–4.6 (m, 8 H), 5 (br s, 1 H).

Anal. Calcd for $C_{24}H_{45}PO_6$: C, 62.58; H, 9.85. Found: C, 62.91; H, 9.73.

Physical and Analytical Data for Enol Ethers 2. 1,1-Diphenyl-2-(2-tetrahydropyranyloxy)ethene (24): mp 81–82 °C; NMR δ 1.4–2 (m, 6 H), 3.4–4.1 (m, 2 H), 5.09 (br s, 1 H), 6.77 (s, 1 H), 7.1–7.85 (m, 10 H); mass spectrum (70 eV), m/e 280 (M^+).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.11; H, 7.31.

1,1-Diphenyl-2-(*tert*-butyldimethylsilyloxy)ethene (25): oil; NMR δ 0.05 (s, 6 H), 0.93 (s, 9 H), 5.82 (s, 1 H), 7.15–7.55 (m, 1 H).

Anal. Calcd for $C_{20}H_{26}SiO$: C, 77.36; H, 8.44. Found: C, 77.61; H, 8.56.

1,1-Diphenyl-2-(2-methoxyethoxy)ethene (26): oil; NMR δ 3.32 (s, 3 H, OCH_3), 3.45–3.7 (m, 2 H), 3.87–4.15 (m, 2 H), 6.53 (s, 1 H), 7.1–7.55 (m, 10 H); mass spectrum (70 eV), m/e 254 (M^+).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 79.93; H, 7.22.

2-Phenyl-1-(2-tetrahydropyranyloxy)propene (27): oil; NMR δ 1.15–1.9 (m, 6 H), 1.95 and 2.05 (2 d, 3 H, $J \simeq$ 1.5 Hz), 3.2–4.15 (m, 2 H), 5.02 (br s, 1 H), 6.43 and 6.73 (2 q, ratio 5:7, 1 H, $J \simeq$ 1.5 Hz), 7.1–7.8 (m, 5 H); mass spectrum (70 eV), m/e 218 (M^+).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.29; H, 7.98.

2-Phenyl-1-(2-methoxyethoxy)propene (28): oil; NMR δ 1.88 and 2.0 (2 d, 3 H, $J \simeq$ 1.5 Hz), 3.31 (br s, 3 H, OCH_3), 3.4–3.68 (m, 2 H), 3.75–4.18 (m, 2 H), 6.17 and 6.6 (2 m, ratio 2:3, 1 H), 7.1–7.85 (m, 5 H); mass spectrum (70 eV), m/e 192 (M^+).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.12; H, 8.4.

(2-Tetrahydropyranyloxy)methylenecyclohexane (29): oil; NMR δ 1.2–2.4 (m, 16 H), 3.3–4.1 (m, 2 H), 4.83 (br s, 1 H), 6.0 (br s, 1 H); mass spectrum (70 eV), m/e 196 (M^+).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.5; H, 10.35.

(2-Methoxyethoxy)methylenecyclohexane (30): oil; NMR δ 1.15–2.4 (m, 10 H), 3.39 (s, 3 H, OCH_3), 3.35–3.95 (m, 4 H), 5.85 (m, 1 H).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.31; H, 10.75.

(2-Tetrahydropyranyloxy)methylenecyclopentane (31): oil; NMR δ 1.2–2.55 (m, 14 H), 3.3–4.15 (m, 2 H) 4.85 (br s, 1 H), 6.17 (m, 1 H); mass spectrum (70 eV), m/e 182 (M^+).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.99. Found: C, 72.66; H, 10.07.

1-(2-Naphthyl)-2-(2-methoxyethoxy)ethene (32): oil; mass spectrum (70 eV), m/e 228 (M^+).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.92; H, 7.16.

1-(2-Methyl-1-oxo-1,2-dihydro-4-isoquinolyl)-2-(2-tetrahydropyranyloxy)ethene (33): oil; NMR δ 1.3–2 (m, 6 H), 3.58 and 3.63 (2 s, ratio ca. 3:1, 3 H, NCH_3), 3.4–4.2 (m, 2 H), 5.1 (m, 1 H), 5.58 (d, J_{cis} = 7 Hz), 6.22 (dd, J_{trans} = 12 Hz, J = 1 Hz), 6.57 (d, J_{cis} = 7 Hz), 6.78 (d, J_{trans} = 12 Hz), 7.03 (d, 1 H, J = 1 Hz), 7.3–7.9 (m, 3 H), 8.33–8.62 (m, 1 H); peaks centered at δ 5.58 and 6.22 were in a relative ratio of 1:3 and integrated for 1 H; peaks centered at δ 6.57 and 6.78 were in a relative ratio of 1:3 and integrated for 1 H; mass spectrum (70 eV),m/e 285 (M^+).

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.82; H, 6.9; N, 4.77.

1-Phenyl-4-(2-tetrahydropyranyloxy)-1,3-butadiene (34): oil; NMR δ 1.2–2 (m, 6 H), 3.3–4.3 (m, 2 H), 4.99 (br s, 1 H), 5.15–7.05 (m, 3 H), 7.1–7.65 (m, 6 H); mass spectrum (70 eV), m/e 230 (M^+).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.5; H, 7.62.

1,3-Diphenyl-4-(2-tetrahydropyranyloxy)-1,3-butadiene (35): oil; NMR δ 1.2–2 (m, 6 H), 3.3–4.1 (m, 2 H), 5.03 (m, 1 H), 6.2 and 6.43 (2 d, ratio 2:3, 1 H, J = 13 Hz), 6.47 and 6.77 (2 s, ratio 2:3, 1 H), 7–8.2 (m, 11 H); mass spectrum (70 eV), m/e 306 (M^+).

Anal. Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 81.97; H, 7.11.

5-Methyl-12-(carbophenoxy)-9-(2-tetrahydropyranyloxy)methylene-6,10-imino-9*H*-cyclooct[*b*]indole (36): oil; NMR δ 1.3–2.9 (m, 12 H), 3.6 (s, 3 H), 3.8–4.2 (m, 2 H), 4.8–5.2 (m, 1 H), 5.5–6.2 (m, 3 H), 7.0–7.6 (m, 9 H); mass spectrum (70 eV), m/e 458 (M^+).

Anal. Calcd for $C_{28}H_{30}N_2O_4$: C, 73.34; H, 6.59; N, 6.11. Found: C, 72.97; H, 7.1; N, 6.17.

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Registry No. 6 (R = C_4H_9), 24630-66-8; 6 (R = C_2H_5), 3084-40-0; **7a**, 70080-15-8; **7b**, 71885-51-3; **7c**, 71885-52-4; **7d**, 70080-14-7; **11**, 70079-97-9; **12**, 71885-53-5; **13**, 70079-96-8; **14**, 70079-99-1; **15**, 70079-98-0; **16**, 70080-01-2; **17**, 71885-54-6; **18**, 70080-00-1; **19**, 70080-03-4; **20**, 70080-02-3; **21**, 70080-04-5; **22**, 71885-55-7; **23**, 71885-56-8; **24**, 70080-10-3; **25**, 71885-57-9; **26**, 70080-05-6; **27**, 70080-11-4; **28**, 70080-06-7; **29**, 70080-12-5; **30**, 70080-07-8; **31**, 70080-08-9; **32**, 70080-09-0; **33**, 71885-58-0; **34**, 71885-59-1; **35**, 71885-60-4; **36**, 71885-61-5; **37**, 71885-62-6; diphenylacetaldehyde, 947-91-1; 2-phenylpropanal, 93-53-8; cyclohexanecarboxaldehyde, 2043-61-0; cyclopentanecarboxaldehyde, 872-53-7; 2-(2-naphthyl)-acetaldehyde, 70080-13-6; 2-(2-methyl-1-oxo-1,2-dihydro-4-isoquinolyl)acetaldehyde, 71885-63-7; dibutyl phosphite, 1809-19-4; diethyl phosphite, 762-04-9; triethyl phosphite, 122-52-1; benzophenone, 119-61-9; acetophenone, 98-86-2; cyclohexanone, 108-94-1; cyclopentanone, 120-92-3; 2-naphthaldehyde, 66-99-9; 4-formal-2-methyl-1-oxo-1,2-dihydroisoquinoline, 31588-53-1; cinnamaldehyde, 104-55-2; chalcone, 94-41-7; 5-methyl-12-(carbophenoxy)-9-oxo-6,10-imino-9*H*-cycloact[*b*]indole, 71885-64-8; camphor, 76-22-2.

Terretonin, a Toxic Compound from *Aspergillus terreus*

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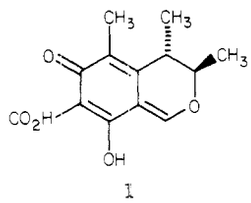
The isolation and structure determination of terretonin (7), a new, unique toxic metabolite of *Aspergillus terreus*, is reported. The structural characterization included UV, IR, MS, CD, ^1H NMR, ^{13}C NMR, and X-ray analysis.

Recently, the practice of baling hay in large (500 kg) round or square bales has become popular. Since these bales are generally stored in direct contact with the weather, they become contaminated with fungi. We isolated a strain of *Aspergillus terreus* (NRRL 6273) from one of these bales in a screening program for the detection of toxigenic fungi.[1] *A. terreus* is known to produce the toxins citrinin (**1**)[2] and patulin (**2**)[3] and also a variety of



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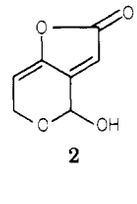

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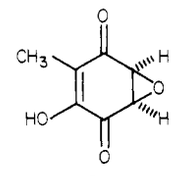
metabolites including terreic acid (**3**),[4] quadrone (**4**),[5] aspterreic acid (**5**),[6] and aspergillide B1 (**6**).[7] We wish to report the isolation and structure of a new, unique metabolite, terretonin (**7**), from this fungus.[13]

Results and Discussion

A molecular formula of $C_{26}H_{32}O_9$ was determined for **7** by high-resolution mass spectrometry and elemental



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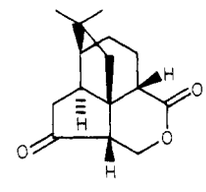

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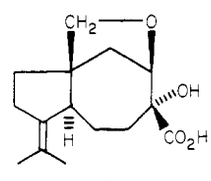

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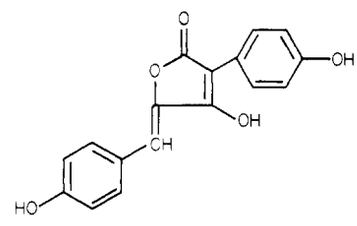

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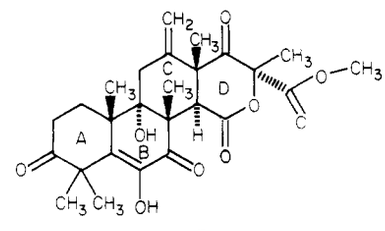

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analysis. UV analysis indicated that **7** possessed one chromophore containing two double bonds (later shown to be an α,β-unsaturated ketone) while IR analysis indicated that the compound contained at least two hydroxyls, two esters, and several ketones. Preliminary ^1H NMR experiments indicated that a structure for **7** would have to include six methyl groups and one methoxy group, as well as a vinylidine moiety. In addition, the proton-decoupled ^{13}C NMR chemical shifts (Table I) show 24 individual resonances, including two double bonds with one

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