υ for various ranges of the functions tested. Refinement was terminated when all parameter shifts were less than 0.10 of their corresponding standard deviations. The final value of R for all 2515 reflections was 0.057 and that for R_w, where $R_w = \sum W_F^{1/2}[F_o - F_c]/\sum W_F^{1/2}|F_o|$, was 0.077.

Acknowledgment. Grateful acknowledgment is given to the National Institutes of Health of the USPHS for a grant from the National Cancer Institute (Grant No. CA 22770-03 to K.D.B. and Grant No. CA 17562 to D.v.d.H.) for partial support of this research.

Registry No. 1a, 22842-37-1; **1b**, 1072-72-6; **1c**, 22842-41-7; **1d**, 18456-44-5; **4a**, 73321-76-3; **4b**, 73321-78-5; **4c**, 73321-77-4; **4d**, 78804-16-7; **6a**, 52978-85-5; **6b**, 67464-47-5; **6c**, 67464-48-6; **6d**, 67464-49-7; 7b, 67464-50-0; **8b**, 78050-22-3; ethyl α-(bromomethyl)acrylate, 17435-72-2.

Supplementary Material Available: Figures 2–4 and tables containing positional parameters for nonhydrogen atoms, anisotropic thermal parameters, hydrogen positional, thermal parameters, and a listing of observed and calculated structure factor amplitudes for **4c** (14 pages). Ordering information is given on any current masthead page.

Notes

Synthesis of 5,5-Dichloro-4-pentenoic Acid by the Wittig Reaction with Bromotrichloromethane and Triphenylphosphine

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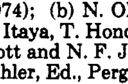
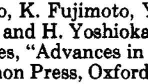
Received October 28, 1980

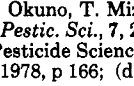
In 1973, Elliott et al.[1] described the insecticidal properties of permethrin, an important synthetic pyrethroid derived from 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylic acid (**1**). In subsequent studies on the acid moiety of these insecticides, a number of investigators have shown that the intact cyclopropane ring was an unnecessary structural feature for high activity.[2] For example, the cyano(3-phenoxyphenyl)methyl ester of (±)-4-chloro-α-(1-methylethyl)benzeneacetic acid, commonly known as fenvalerate, has reached the commercial stage of development. Despite these facts, few published reports have dealt specifically with analogues of **1** in which the cyclopropane ring system was absent. At the onset of this work, it was decided that 5,5-dichloro-4-pentenoic acid (**2**) would serve as a useful intermediate for structure–activity studies on synthetic pyrethroid insecticides. To my knowledge, **2** has not been described in the recent literature, but a series of insecticidally active esters of this acid, with substituents at the α (C-2) position, have recently been patented.[3] These patents have encouraged the publication of the chemistry that has been explored during the synthesis of **2**.



1



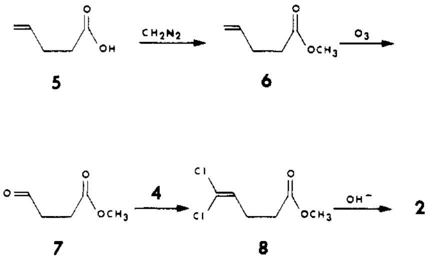
2



3

On the assumption that the dichloromethylene group (=CCl$_2$) could be introduced into 4-oxobutanoic acid (**3**)[4] by the Wittig reaction with (dichloromethylene)triphenylphosphorane (**4**), now prepared to advantage by the interaction of CBrCl$_3$ with Ph$_3$P (eq 1)[5] rather than CCl$_4$ with Ph$_3$P,[6] then the synthesis of **2** appeared to be a straightforward task, at least by comparison to the synthesis of **1** by similar approaches.[7] In this work, **2** was obtained by use of the Wittig reaction, when **4** was generated according to eq 1.

Scheme I



$$2Ph_3P + CBrCl_3 \rightarrow \underset{\mathbf{4}}{Ph_3P{=}CCl_2} + Ph_3PBrCl \qquad (1)$$

4-Pentenoic acid (**5**) was the preferred starting material for the synthesis of **2** (Scheme I). Ozonolysis of methyl ester (**6**) in methylene chloride solution at −78 °C gave the desired ester aldehyde, methyl 4-oxobutanoate (**7**).[8] Either Ph$_3$P[9] or Me$_2$S[10] was employed as reducing agent, allowing the isolation of pure **7** in yields of 45–60%. The properties of distilled samples of **7** agreed with those reported in the literature.[11]

The Wittig reaction on **7**, performed by allowing the aldehyde to interact with a mixture of CBrCl$_3$ and Ph$_3$P

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(1) M. Elliott, A. W. Farnham, N. F. Janes, P. H. Needham, D. A. Pulman, and J. H. Stevenson, *Nature (London)*, **246**, 169 (1973).

(2) See, for example: (a) N. Ohno, K. Fujimoto, Y. Okuno, T. Mizutani, M. Hirano, N. Itaya, T. Honda, and H. Yoshioka, *Agric. Biol. Chem.*, **38**, 881 (1974); (b) N. Ohno, K. Fujimoto, Y. Okuno, T. Mizutani, M. Hirano, N. Itaya, T. Honda, and H. Yoshioka, *Pestic. Sci.*, **7**, 241 (1976); (c) M. Elliott and N. F. Janes, "Advances in Pesticide Science", Part 2, H. Geissbühler, Ed., Pergamon Press, Oxford, 1978, p 166; (d) J. Menn, *J. Agric. Food Chem.*, **28**, 2 (1980).

(3) (a) P. Winternitz, German Patent 2800073 (1978); *Chem. Abstr.*, **89**, 163246m (1978); (b) F. Mori and Y. Omura, German Patent 2810031 (1978); *Chem. Abstr.*, **90**, 71915w (1979).

(4) C. G. Wermuth, *J. Org. Chem.*, **44**, 2406 (1979).

(5) B. A. Clement and R. L. Soulen, *J. Org. Chem.*, **41**, 556 (1976).

(6) (a) A. J. Speziale and K. W. Ratts, *J. Am. Chem. Soc.*, **84**, 854 (1962); (b) R. Rabinowitz and R. Marcus, *J. Am. Chem. Soc.*, **84**, 1312 (1962); (c) C. Raulet and E. Levas, *C. R. Acad. Sci., Ser. C*, 1467 (1970).

(7) (a) M. Elliott, N. F. Janes, and D. A. Pulman, *J. Chem. Soc., Perkin Trans. 1*, 2470 (1974); (b) M. Elliott, N. F. Janes, D. A. Pulman, L. C. Gaughan, T. Unai, and J. E. Casida, *J. Agric. Food Chem.*, **24**, 270 (1976); (c) I. Nakatsuka, F. Shono, and A. Yoshitake, *J. Labelled Compd. Radiopharm.*, **13**, 561 (1977); (d) W. G. Taylor, *Synthesis*, 554 (1980).

(8) For related ozonolyses, see: (a) P. L. Stotter and J. B. Eppner, *Tetrahedron Lett.*, 2417 (1973); (b) H. Zamarlik, *C. R. Acad. Sci., Ser. C*, 1138 (1970).

(9) W. G. Taylor, *J. Org. Chem.*, **44**, 1020 (1979).

(10) R. M. Coates, D. A. Ley, and P. L. Cavender, *J. Org. Chem.*, **43**, 4915 (1978).

(11) H. Sumitoto, K. Kobayashi, and T. Saji, *J. Polym. Sci., Polym. Chem. Ed.*, **10**, 3421 (1972).

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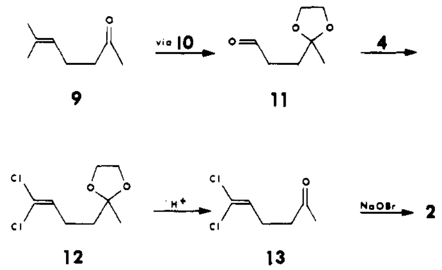
Scheme II



in benzene or THF solution, gave methyl 5,5-dichloro-4-pentenoate (**8**) in yields ranging from 40 to 60% (after distillation). An analytically pure sample of **8** was obtained by column chromatography. The IR spectrum showed a carbonyl absorption at 1740 cm^{-1} for the ester group and a weaker band at 1625 cm^{-1} for the double bond stretching vibration of the dichloroethenyl group. The NMR and mass spectra were also in agreement with **8**. Conditions for the hydrolysis of this ester followed closely the method of Nakatsuka et al.,[7] except that high temperatures were avoided. Under optimum conditions (KOH, MeOH, 0–20 °C for 2.5 h), the acid **2** was isolated in a yield of 90%. Yields were from 40 to 50% when **8** was hydrolyzed under refluxing conditions. The structure of **2** was confirmed from its IR and NMR spectra and from the synthesis of this acid by another route.

By starting with 6-methyl-5-hepten-2-one (**9**), **2** was also obtained by the sequence of reactions shown in Scheme II. The preparation of 6-methyl-5-hepten-2-one ethylene ketal (**10**) and its conversion with ozone to ketal aldehyde (**11**) followed a literature method.[9] The intermediate **11** gave 6,6-dichloro-5-hexen-2-one ethylene ketal (**12**) by the Wittig reaction with $CBrCl_3$ and Ph_3P. Treatment of crude **12** with aqueous acid in THF solution, followed by workup and distillation, gave the desired 6,6-dichloro-5-hexen-2-one (**13**) in yields of 50–75%. A haloform reaction on **13**, employing sodium hypobromite in dioxane and water,[12] gave a mixture of products. A product was isolated by column chromatography that showed the same NMR spectrum as **2**. The methyl ester of this acid was also identical to **8** from Scheme I.

Since the synthesis of **2** depended on success with the Wittig reaction, some features of this reaction were established. Certain aldehydes,[13] including isomeric precursors of **1** synthesized in this laboratory,[7] have recently been shown to give high yields of 1,1-dichloroolefins when subjected to small-scale Wittig reactions with $CBrCl_3$ and hexamethylphosphorous triamide (HMPT). It was therefore predicted that the method with $CBrCl_3$ and HMPT would offer advantages over the method with $CBrCl_3$ and Ph_3P. With $CBrCl_3$ and HMPT, **7** gave **8** in yields that never exceeded 20%. These results, combined with the necessity for dilute solutions of the reagents,[13] precluded the further use of HMPT in the present, larger scale work.

Selection of optimum conditions for Wittig reactions with $CBrCl_3$ and Ph_3P came from modifying the literature procedure[5] in various ways. In experiments with **7**, benzene was compared with THF as the solvent. Although the yields were about the same, benzene was preferred because an insoluble precipitate of Ph_3P and Ph_3PO usually formed more readily, thus facilitating the removal of these interfering products by simple filtration. Nearly a threefold excess of $CBrCl_3$ was required, despite the stoichiometry of eq 1, and at least 12 h at room temperature was necessary for the completion of these reactions. Side products formed in the Wittig reactions amounted to 10–15% of the volatile components in crude reaction mixtures.[14]

Experimental Section

Melting points (taken on a Fisher hot-stage apparatus) and boiling points (recorded during distillations under reduced pressure) are uncorrected. Infrared spectra were taken as liquid films on a Perkin-Elmer Model 137 Infracord spectrophotometer. Proton nuclear magnetic resonance (NMR) spectra were obtained on a Varian EM-360A spectrometer, using $CDCl_3$ as the solvent. The chemical shifts are expressed as δ values (ppm) to Me_4Si as an internal standard. Gas–liquid chromatography (GC) was performed on a Hewlett-Packard Model 5838A instrument equipped with a 1.2 m × 4 mm i.d. glass column packed with 3% or 5% OV-101 on acid-washed DMCS-treated Chromosorb 750. Electron impact mass spectra (70 eV) were obtained with a Hewlett-Packard Model 5985B instrument. Elemental analyses were obtained from Dr. C. Daessle, Montreal, Quebec.

Benzene was dried over sodium and distilled before use. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ and then redistilled from sodium and benzophenone. Distillations and Wittig reactions were performed under N_2 and Ar atmospheres, respectively. Bromotrichloromethane (spectrophotometric grade) and triphenylphosphine were used as received from Aldrich Chemical Co. 4-Pentenoic acid was obtained from K & K Laboratories or from Pfaltz and Bauer, Inc.

Methyl 4-Pentenoate (6). **5** (22.25 g, 222 mmol) in ether (50 mL) was reacted with diazomethane (prepared from Diazald) in the usual manner to give 19.25 g (75.9%) of **6** as a colorless oil: bp 49–53 °C (33 mm) (lit.[15] bp 120–122 °C at 760 mm); IR 1740 (C=O) and 1650 cm^{-1} (C=C); NMR δ 6.13–4.83 (m, H_2C=CH) 3.70 (s, OCH_3), 2.67–2.27 (m, CH_2CH_2); mass spectrum, *m/e* (rel intensity) 114 (M^+, 27.5), 55 (100).

Methyl 4-Oxobutanoate (7). With an ozonolysis apparatus described previously,[9] ester **6** (10.0 g, 87 mmol) in methylene chloride (200 mL) was cooled to −78 °C and ozone was slowly introduced into the solution until a blue color was evident. The mixute was swept with N_2 during 1 h and then Ph_3P (10.5 g) was added. The mixture was allowed to come to room temperature gradually and the solvent was removed on a rotary evaporator. Hexane (150 mL) was added with stirring and a white crystalline material was removed by filtration. The filtrate was dried ($MgSO_4$) and concentrated on a rotary evaporator. Distillation under reduced pressure gave 6.16 g (60.6%) of **7** as a colorless oil: bp 70–72 °C (20 mm) (lit.[11] bp 57.5–58 °C at 6 mm); the 2,4-dinitrophenylhydrazone derivative, recrystallized from methanol, had mp 126–129 °C (lit.[11] mp 129–130 °C); IR 1740 cm^{-1} (C=O); NMR δ 9.78 (s, CHO), 3.68 (s, OCH_3), 3.03–2.43 (m, CH_2CH_2); mass spectrum, *m/e* (rel intensity) 116 (M^+, 0), 88 (100).

General Procedure for Wittig Reactions. The aldehyde (1 equiv) was added by syringe to a mixture of $CBrCl_3$ (2.7 equiv) and Ph_3P (2 equiv). The mixture was stirred in an ice bath (∼4 h) and then at room temperature for 16–40 h (until GC or IR on aliquots showed the consumption of the aldehyde). A solid precipitate in the brown mixture usually formed, which was removed by filtration. If an insoluble oil was present, the solvent was decanted and the oil was washed several times with warm benzene or THF. The filtrate or combined washes were concentrated on a rotary evaporator and the residue was stirred well with hexane. An off-white precipitate was removed by filtration and washed with hexane. The hexane filtrate was dried ($MgSO_4$), evaporated, and then distilled under vacuum to yield the product.

Methyl 5,5-Dichloro-4-pentenoate (8). With the general Wittig procedure with benzene (50 mL) as the solvent, **7** (5.4 g, 46.5 mmol) gave 4.9 g of a crude product. Distillation under

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(12) (a) G. W. Shaffer, A. B. Doerr, and K. L. Purzycki, *J. Org. Chem.*, **37**, 25 (1972); (b) E. E. van Tamelen, J. Webber, G. P. Schiemenz, and W. Barker, *Bioorg. Chem.*, **5**, 283 (1976).

(13) W. G. Salmond, *Tetrahedron Lett.*, 1239 (1977).

(14) The identity of the side products is currently under investigation.

(15) H. K. Hall, J. P. Schaefer, and R. J. Spanggord, *J. Org. Chem.*, **37**, 3069 (1972).

reduced pressure gave 3.5 g (41% yield) of **8** with a purity by GC of 87%. Column chromatography (silicAR cc-7) with petroleum ether (bp 30-60 °C) followed by redistillation gave an analytically pure sample as a colorless oil: bp 103-105 °C (21 mmHg); IR 1740 (C=O) and 1625 cm^{-1} (C=C); NMR δ 5.88 (ragged t, C=CH), 3.70 (s, OCH_3), 2.67-2.20 (m, CH_2CH_2); mass spectrum, *m/e* (rel intensity) 182 (M^+ for Cl = 35, 20.5), 122 (100). Anal. Calcd for $C_6H_8Cl_2O_2$: C, 39.37; H, 4.41; Cl, 38.74. Found: C, 39.56; H, 4.34; Cl, 38.51.

With THF as the solvent, **7** (10 mmol) gave **8** in a 59% yield after one distillation. The purity of the distilled sample was 85%.

5,5-Dichloro-4-pentenoic Acid (2). A mixture of pure **8** (0.549 g, 3 mmol) in MeOH (6 mL) and KOH (1.18 g, 21 mmol) was stirred at 5 °C for 30 min and then at room temperature for 2 h (Ar atmosphere). The mixture was concentrated on a rotary evaporator and the semisolid residue was dissolved in water. The aqueous phase was washed with hexane, acidified to pH 1 with 1 N HCl, and extracted with methylene chloride. The organic phase was washed with a saturated solution of NaCl and dried (Na_2SO_4). Evaporation of the solvent gave **2** (456 mg, 90%) as a colorless oil: IR 1710 (C=O) and 1625 cm^{-1} (C=C); NMR δ 9.92 (s, COOH, exchanged with D_2O), 5.92 (m, C=CH), 2.73-2.20 (m, CH_2CH_2). Acid **2** was found to slowly decompose on storage at room temperature as indicated from the appearance of NMR signals near 3.5 ppm. At 4 °C, the compound appeared to be stable for several months. After **2** (400 mg) was stirred in hexane (10 mL) and 1 N sodium carbonate (3 mL) for 1 h, the aqueous phase was removed and treated with methanol (30 mL) and THF (60 mL). The mixture was cooled at 4 °C, then filtered, and evaporated. Lyophilization of the concentrated filtrate gave a sodium salt of **2** (390 mg) as a white, crystalline power: mp 180-185 °C.

6,6-Dichloro-5-hexen-2-one (13). According to the general Wittig procedure, **11** (11.5 g, 80 mmol)[9] was reacted with **4** in benzene solution (100 mL) for 24 h. The crude product (~18.5 g) isolated after filtration and evaporation of the solvents showed two main peaks by GC. This sample (a mixture of **12** and **13**) was dissolved in THF (150 mL) and 5 N HCl (50 mL) was added. After 4 h at room temperature, the solution was neutralized to pH 7 with $NaHCO_3$. The THF was removed on a rotary evaporator and a saturated solution of NaCl (80 mL) was added. The product was extracted with ether and the organic extract was dried ($MgSO_4$). Distillation under reduced pressure gave **13** (9.44 g, 70.8%) as a nearly colorless oil: bp 37-38 °C (0.2 mm); IR 1715 (C=O) and 1620 cm^1 (C=C); NMR δ 5.88 (ragged t, C=CH), 2.80-2.33 (m, CH_2CH_2), 2.17 (s, CH_3); mass spectrum, *m/e* (rel intensity) 166 (M^+, 35.5), 131 (100). Anal. Calcd for $C_6H_8Cl_2O$: C, 43.14; H, 4.83; Cl, 42.45. Found: C, 43.44; H, 5.02; Cl, 42.21.

This experiment was repeated with 39, 63.8, and 69.4 mmol of **11**. The respective yields, based on distilled samples of **13**, were 50, 60, and 75%. The purity by GC was ~85%.

Haloform Oxidation of 13. Ketone **13** (13.55 g, 81 mmol) was dissolved in dioxane (100 mL) and cooled to 2 °C. To this solution was added dropwise during 15 min a cold solution of NaOBr, prepared by adding Br_2 (51.62 g, 323 mmol) to an ice-cold solution of NaOH (38.93 g) in water (200 mL). The mixture was stirred mechanically for 1 h and then at room temperature for 5 h. A solution of sodium sulfite (9.9 g) in water (90 mL) was added to the faint-yellow mixture and the pH was adjusted to 12 with NaOH pellets. After extraction with ether, the aqueous phase was adjusted to pH 2 with HCl. The mixture was saturated with NaCl and then extracted with ether. The combined ether extracts were washed with a saturated solution of NaCl and dried ($MgSO_4$). Removal of the dioxane by distillation left a crude yellow product (9.2 g). A portion of the residue was purified by column chromatography (silicAR cc-7). A middle fraction, obtained by elution with hexane-ether (5:1, v/v), gave 5,5-dichloro-4-pentenoic acid (20.1% yield) as determined by NMR spectral comparison to **2** from Scheme I.

A sample of **2** (100 mg) was treated with 10 mL of a methanolic solution of HCl and heated under reflux for 15 h. After addition of water, the mixture was extracted with hexane. Evaporation of the dried ($MgSO_4$) organic extracts gave 104 mg of an oil (63% pure by GC). The major component was isolated by column chromatography (silicAR cc-7) with hexane and was identified as **8** by GC and mass spectral comparison to **8** obtained by the sequence in Scheme I.

Acknowledgment. I thank Mr. Art Hewitt for technical assistance and Mr. Jim Elder for recording the mass spectra.

Registry No. 2, 4189-05-3; **2**·Na, 78019-16-6; **4**, 6779-08-4; **5**, 591-80-0; **6**, 818-57-5; **7**, 13865-19-5; **7** 2,4-dinitrophenylhydrazone, 15903-35-2; **8**, 38666-11-4; 11, 24108-29-0; **12**, 78019-17-7; **13**, 57054-18-9; $CBrCl_3$, 75-62-7.

Selective Reductive Carbonyl Couplings with Titanium

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Considerable interest recently has been shown in the reductive coupling of ketones and aldehydes to olefins, using low-valent titanium reagents,[1] accessible from $TiCl_3$ or $TiCl_4$ by reduction with Zn,[3,4] Mg,[5] Zn-Cu couple,[6] K, Li,[6a,7] or $LiAlH_4$.[8] Intramolecular dicarbonyl coupling to cycloalkenes is also possible in high yield, including medium sized rings.[6a] This formal reverse of a double bond ozonolysis appears to have great synthetic potential. However, the reagent also reacts with other functional groups.[9] Its use was therefore assumed to be limited to cases where functional groups other than alcohols, ethers, and olefins are not present.[6a]

We now report our results on the selective reductive coupling of aromatic aldehydes and ketones having carboxylate or tosylate ester functionalities to the corresponding stilbenes (Schemes I and II). Contrary to what was expected on the basis of previous works,[5,6a,7] in most cases the ester groups remained unaffected under the reaction conditions.

In connection with another project we needed to prepare the phenolic stilbene **1**. The most simple approach seemed to be the reductive coupling of a suitably protected benzaldehyde. We first tried the *O*-benzyl-protected benzaldehyde **2a**, the corresponding stilbene **3a** resulting in a high yield on reaction of **2a** with $TiCl_3$ and Zn-Cu.

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(1) The so-called low-valent titanium species seem in most cases to be active Ti^0, as can be inferred from the work of R. D. Rieke, *Acc. Chem. Res.*, **10**, 301 (1977) and ref 6a. (π-$C_6H_6)_2$Ti^0 has also been used.[2]

(2) H. Ledon, I. Tkatchenko, and D. Young, *Tetrahedron Lett.*, 173 (1979).

(3) T. Mukaiyama, T. Sato, and J. Hanna, *Chem. Lett.*, 1041 (1973); D. Lenoir and P. Lemmon, *Chem. Ber.*, **113**, 3112 (1980).

(4) J. Drabowicz and M. Mikolajczyk, *Synthesis*, 138 (1978).

(5) S. Tyrlik and I. Wolochowick, *Bull. Soc. Chim. Fr.*, 2147 (1973).

(6) (a) J. E. McMurry, M. P. Fleming, K. L. Kees, and L. R. Krepski, *J. Org. Chem.*, **43**, 3255 (1978); (b) J. A. Marshall, R. E. Bierenbaum, and K. H. Chung, *Tetrahedron Lett.*, 2081 (1979).

(7) S. C. Welch and M. Walters, *J. Org. Chem.*, **43**, 4797 (1978).

(8) J. E. McMurry and M. P. Fleming, *J. Am. Chem. Soc.*, **96**, 4708 (1974); H. Wynberg, K. Lammerstsma, and L. A. Hulshot, *Tetrahedron Lett.*, 3749 (1975); R. F. Langler and T. T. Tidwell, *ibid.*, 777 (1975); D. S. Bomse and T. H. Morton, *ibid.*, 781 (1975); A. L. Baumstark, E. J. H. Bechara and H. J. Semigram, **ibid.**, 3265 (1976); P. D. Mollere, K. N. Houk, D. L. Bomse, and T. H. Morton, *J. Am. Chem. Soc.*, **98**, 4732 (1976).

(9) Low-valent titanium species are known to react with esters,[5,6a,7] acid chlorides, 1,2-diketones, α-bromo and α-phenyl sulfenyl ketone enolates, ketals[6a], thioketals, organic halides[10], epoxides[2,10], sulfoxides,[4] and enol phosphates.[7]

(10) T. Mukaiyama, *Angew Chem., Int. Ed. Engl.*, **16**, 817 (1977), and references therein.

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