Substituting the last P_f equation into the last G_f equation,

$$[G_f] = [G_t]/(1 + (1/K_1 + 2[G_f]/(K_1K_2))([P_t]/(1 + [G_f]/K_1 + [G_f][G_f]/(K_1K_2))))$$

This simplifies to

$$f = 0 = [G_f]^3 + (K_2 + 2[P_t] - [G_t])[G_f]^2 + (K_1 + [P_t] - [G_t])K_2[G_f] - K_1K_2[G_t]$$

and

$$f_1 = d(f)/d[G_f]$$

Then Newton's method[9] is used to calculate the $[G_f]$ by

$$[G_f] = [G_f] - f/f_1$$

and this is repeated until f is equal to zero. Then $[P_f]$, $[PG]$, and $[PG_2]$ are calculated. With the concentration of the species calculated, a theoretical point (cp) is calculated by

$$ep(1) = \text{experimental point when } [G_t] = 0$$

$$ep(n) = \text{experimental point when } [G_t] = 20$$

ep = experimental point at the $[P_t]$ and $[G_t]$ used in the calculation for the concentration of species.

$$cp = ep(1)([P_f] + [PG])/[P_t] + ep(n)[PG_2]/[P_t]$$

The quality of the fit is determined by

$$ss = \sum_1^n (cp - ep)^2$$

The fit is optimized by varying K_1 and K_2. All data sets gave the same qualitative K's.

Registry No. Z-Gla-OMe, 96095-90-8; Z-Gla-Arg-OMe, 96095-90-8; guanidine, 113-00-8; L-arginine, 74-79-3; γ-carboxyglutamic acid, 53861-57-7.

(11) Tuhy, P. M.; Bloom, J. W.; Mann, K. G. *Biochemistry* **1979**, *18*, 5842–5848.

Notes

Reaction of Some 2,3-Steroidal Epoxides with Tri-*n*-butyl(carbethoxymethylidene)phosphorane. Formation of A-Nor Derivatives

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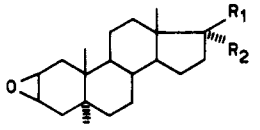
Cyclic epoxides have previously been shown to react with tri-*n*-butyl(carbethoxymethylidene)phosphorane (1) to yield α,β-unsaturated esters in which a ring contraction occurred because of carbon migration; cyclopropyl derivates are formed in minor amounts and in the case of cyclopentene oxide a cyclopropyl derivative is the main reaction product.[1]

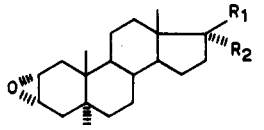
In this note we report the reaction of 1[2] with the 2,3-steroidal epoxides **2**–**6**[3] in refluxing toluene (Chart I).

2β,3-Epoxy-5α-cholestane (**2**) reacts with 1 (epoxide/phosphorane 1:2 molar ratio; reaction time 24 h) to give compound **7** and **8** with satisfactory yields. If the reaction is carried out by using a 1:1 molar ratio, the reaction mixture contains compounds **7** and **8** and aldehyde **9**.

Chart I

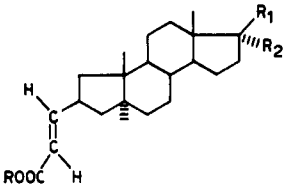


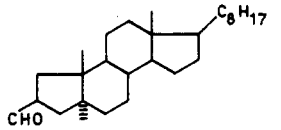
	R_1	R_2
2	C_8H_{17}	H
3	$OCOCH_3$	H



	R_1	R_2
4	C_8H_{17}	H
5	OCH_2CH_2O	
6	OH	CH_3

Chart II





9

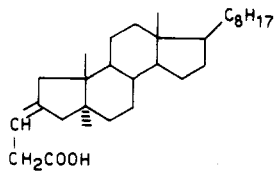
	R	R_1	R_2
7	n-Bu	C_8H_{17}	H
8	C_2H_5	C_8H_{17}	H
10	n-Bu	$OCOCH_3$	H
11	C_2H_5	$OCOCH_3$	H
12	n-Bu	OCH_2CH_2O	
13	C_2H_5	OCH_2CH_2O	
14	n-Bu	OH	CH_3
15	C_2H_5	OH	CH_3

Products **7**, **8**, and **9** are also obtained from the reaction of 2α,3-epoxy-5α-cholestane (**4**); however, this reaction is slower than that of epoxide **2**.

(1) Gerkin R. M.; Rickborn, B. *J. Am. Chem. Soc.* **1967**, *89*, 5850.
(2) Phosphorane 1 was prepared from the corresponding phosphonium salt and a commercial solution of *n*-butyllithium in hexane (1.6 M, Fluka). The phosphonium salt was prepared according to Speziale, A. J.; Bissing, D. E. *J. Am. Chem. Soc.* **1963**, *85*, 3878.
(3) Epoxides examined were prepared by the following methods. (a) Epoxide **2**: Corey, E. J. *J. Am. Chem. Soc.* **1953**, *75*, 4832. (b) Epoxide **3** was prepared by acetylation (acetic anhydride and pyridine at room temperature) of 2β,3-epoxy-5α-androstan-17-ol obtained from the corresponding bromohydrin. (c) Epoxide **4** was obtained from the reaction of 5α-cholest-2-ene with *m*-cloroperbenzoic acid in $CHCl_3$ at room temperature. (d) Epoxides **5** and **6**: Wolf , G. C.; Blickenstaff, R. T. *J. Org. Chem.* **1976**, *41*, 1254.

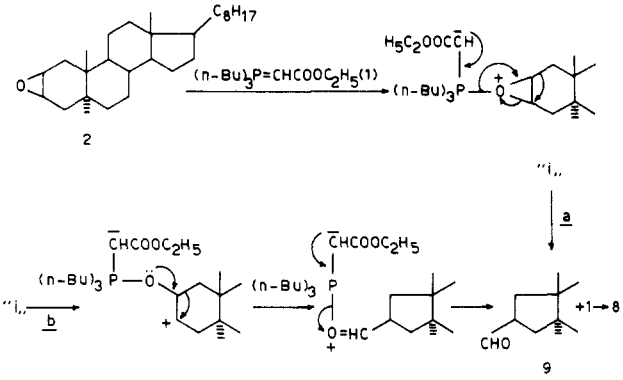
0022-3263/85/1950-2191$01.50/0

Chart III



16

Scheme I



Compounds **10–11**, **12–13**, and **14–15** are obtained from epoxides **3**, **5**, and **6**, respectively[4] (Chart II).

The spectroscopic data (see Experimental Section) are in agreement with the assigned structures; as a matter of fact, the coupling constants of the olefinic protons (J = 16 Hz) allow us to assign the trans configuration to the α,β-unsaturated esters.

Basic hydrolisis in methanol of either **7** or **8** gives a mixture from which we were not able to isolate pure products. The ^{1}HNMR spectrum of the mixture shows the proton signals of the unrearranged α,β-unsaturated acid and of the β,γ-unsaturated acid corresponding to structure **16**;[5] the former is found to predominate when hydrolisis is carried out at 50 °C, the latter when hydrolisis is carried out in refluxing methanol[6] (Chart III).

As to the mechanism of the reaction of phosphorus ylides with epoxides, a nucleophilic displacement of the epoxidic oxygen by the carbanionic center of the ylide was proposed.[1] In our case the isolation of aldehyde **9** suggests that an electrophilic rearrangement of the 2,3-epoxide leads to an aldehyde from which the α,β-unsaturated ester is formed by an ordinary Wittig reaction.

Since no rearrangement takes place when epoxide **2** is treated with tri-*n*-butyl(carbethoxymethylene)-phosphonium bromide or *n*-butyllithium, we believe that the mechanism involves an electrophilic attack by the phosphorus ylide of the epoxide oxygen (see Scheme I). The concurrent or subsequent migration of a carbon ring gives aldehyde **9** (path a or path b). The final reaction is an ordinary Wittig reaction of **9** with ylide **1**.

The formation of *n*-butyl esters is due to the transesterification of the initially formed ethyl ester by *n*-butoxide ions that are present in the butyllithium solution.

The β-configuration of the formyl group in compound **9** was assigned on the basis that aldehyde **9** is reduced by lithium aluminum hydride to give a primary alcohol having the physical and spectral properties of 2β-(hydroxymethyl)-*A*-norcholestane (**17**).[7] The same β-configuration was assigned to the α,β-unsaturated ester groups in compounds **7** and **8**, according to the mechanism proposed for their formation. Moreover, aldehyde **9** was converted into **7** and **8** upon treatment with ylide **1**. Esters **10**, **12**, **14** and **11**, **13**, **15** have spectroscopic properties similar to those of **7** and **8**, respectively. Therefore, the same C_2 configuration was assigned to them.

The trans-olefin formation can be attributed either to a preferred reaction stereochemistry[8] or to a rapid conversion cis → trans.

As to the absence of any detectable α-formyl derivative in the reaction of 2α,3-epoxide **4**, it is probably due to the fact that the α-formyl derivative can isomerize to the β-formyl compound, as observed in the case of 3-substituted cyclopentanecarboxaldehydes.[9]

Experimental Section

Melting points were obtained with a Kofler microscope and are uncorrected. Boiling points were determined by microdistillation. Infrared spectra were recorded in CCl_4 solution; ^{1}H NMR spectra were obtained at 90 MHz using CCl_4 as a solvent and Me_4Si as an internal standard; ^{1}H NMR spectra of compounds **10**, **11**, **14**, and **15** were recorded at 80 MHz in $CDCl_3$ using $CHCl_3$ as an internal standard. Chemical shifts are reported in parts per million (δ). Optical rotations were determined in $CHCl_3$ at room temperature at the concentrations specified. Yields evaluated from starting material correspond to the pure isolated product.

General Procedure for the Reaction of Steroidal Epoxides with Tri-*n*-butyl(carbethoxymethylidene)phosphorane. A solution of *n*-butyllithium[2] in hexane (1 mL) was added in small portions, at room temperature (N_2 atmosphere), to a magnetically stirred solution of tri-*n*-butyl(carbethoxymethylene)phosphonium bromide (1.5. mmol) in dry toluene. Steroidal epoxide (0.8 mmol) was then added rapidly and the solution was refluxed. The reaction mixture was cooled and washed with water. After drying (Na_2SO_4) and evaporation of the solvent, the residue was purified by chromatography on silica gel.

Reaction of Epoxide 2. The reaction time was 24 h. The components of the reaction mixture were isolated by using a mixture of petroleum ether (40–70 °C) and ether (95:5) as eluent. With an epoxide/ylide 1:2 molar ratio, compounds **7** and **8** were obtained with yields of 60% and 30%, respectively. When the molar ratio of the reactants was 1:1, the yields of **7**, **8**, and **9** were 35%, 15%, and 25%, respectively.

Reaction of Epoxide 4. Using the procedure described above, with and epoxide/ylide 1:2 molar ratio, the reaction time was 24 h and products **7** and **8** were isolated with yields of 40% and 15%, respectively. Some starting material (15%) was recovered. Other products were not identified. When the molar ratio was 1:1, the reaction time was 48 h and the yields of **7** and **9** were 25% and 15%, respectively. Ester **8** was isolated in traces, and 15% of the starting material was recovered. Other products were not identified.

Product **7** is a colorless viscous oil (bp 170 °C (0.9 mmHg)): $[\alpha]_D$ +28.7° (*c* 0.38); IR ν_{max} 1715 (C=O α,β-unsaturated ester), 1648, 1160, 1150 cm^{-1}; ^{1}H NMR 2.80 (1 H, br, H-C_2), 4.02 (2 H, t, J = 7 Hz, $OCH_2CH_2CH_2CH_3$), 5.60 (1 H, d, J = 16 Hz, CH=CHCOOR), 6.80 (1 H, dd, J = 16, 8 Hz, CH=CHCOOR); mass spectrum, *m/e* 484 (M^+, base), 469, 456, 331, 330, 329. Anal. Calcd for $C_{33}H_{56}O_2$: C, 81.75; H, 11.64. Found: C, 82.01; H, 11.84.

Product **8** is a colorless viscous oil (bp 150 °C (0.9 mmHg)): $[\alpha]_D$ +12.7° (*c* 0.41); IR ν_{max} 1718 (C=O α,β-unsaturated ester),

(4) Moreover, we examined the reaction of **1** with 3β-methyl-2α,3-epoxy-5α-cholestane and 2β,3-epoxy-5α-androstan-17β-ol; the former was recovered unchanged, the latter gave a complex mixture.

(5) Structure **16** corresponds to two stereoisomers that are not distinguishable by ^{1}H NMR.

(6) The ^{1}H NMR spectrum (in $CDCl_3$) of the mixture shows the following signals: 2.60–3.20 (br and unresolved d, H-C_2 and =$CHCH_2$COOH), 5.45 (br, =$CH$$CH_2$COOH), 5.70 (d, J = 15 Hz, CH=CHCOOH), 7.10 (dd, J = 15, 8 Hz, CH=CHCOOH).

(7) Cava, M. P.; Weintraub, P. M.; Glamkowski, E. J. *J. Org. Chem.* **1966**, *31*, 2015.

(8) In the Wittig reactions, when resonance-stabilized alkylidenephosphoranes are used, the trans olefin formation is favored (Maecker, A. "Organic Reactions", Adams, R., Ed. Wiley: New York, 1965; Vol. 14, pp 313).

(9) McKillop, A.; Hunt, J. D.; Bigham, E.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 3635, note 55.

1650, 1160, 1150 cm^{-1}; ^{1}H NMR 2.80 (1 H, br, H-C$_2$), 4.10 (2 H, q, J = 7 Hz, OCH_2CH$_3$), 5.62 (1 H, d, J = 16 Hz, CH=CHCOOR), 6.88 (1 H, dd, J = 16, 8 Hz, CH=CHCOOR); mass spectrum, m/e 456 (M$^+$, base), 441, 411, 303, 302, 301. Anal. Calcd for $C_{31}H_{52}O_2$: C, 81.52; H, 11.48. Found: C, 81.63; H, 11.45.

Compound **9**, after careful crystallization from methanol, had the following: mp 64–66 °C; $[\alpha]_D$ +11.1° (c 0.53); IR ν_{max} 1720 (C=O), 1380 cm^{-1}; ^{1}H NMR 2.80 (1 H, br, H-C$_2$), 9.58 (1 H, br with splitting, CHO); mass spectrum, m/e 386 (M$^+$, base), 372, 371, 233, 232, 231. Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.90; H, 12.01.

Reaction of Epoxide 3. Using the general procedure with an epoxide/ylide 1:2 molar ratio, the reaction time was 22 h; products **10** and **11** were isolated by using a mixture of hexane and ether (8:2) as eluent. **10** and **11** were obtained with yields of 22% and 22%, respectively; no starting material was recovered and other products were not identified.

Product **10** is a colorless viscous oil (bp 180 °C (0.7 mmHg)): $[\alpha]_D$ +26.0° (c 0.50); IR ν_{max} 1735, 1720 (C=O α,β-unsaturated ester), 1650, 1240, 1040, 1020 cm^{-1}; ^{1}H NMR 2.80 (1 H, br, H-C$_2$), 4.10 (2 H, t, J = 6 Hz, OCH_2CH$_2$CH$_2$CH$_3$), 4.60 (1 H, three unresolved signals, CHOCOCH$_3$), 5.70 (1 H, d with splitting, J = 15 Hz, CH=CHCOOR), 6.93 (1 H, dd, J = 15, 8 Hz, CH=CHCOOR); mass spectrum, m/e 430 (M$^+$), 415, 401, 375, 374, 370, 357, 355, 315, 314, 242, 149 (base). Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.40; H, 9.85.

Product **11** is a colorless viscous oil (bp 165 °C (0.7 mmHg)): $[\alpha]_D$ +26.5° (c 0.45); IR ν_{max} 1735, 1720 (C=O α,β-unsaturated ester), 1650, 1240, 1150, 1040 cm^{-1}; ^{1}H NMR 2.83 (1 H, br, H-C$_2$), 4.18 (2 H, q, J = 7 Hz, OCH_2CH$_3$), 4.60 (1 H, three unresolved signals, CHOCOCH$_3$), 5.73 (1 H, d, J = 15 Hz, CH=CHCOOR), 6.93 (1 H, dd, J = 15, 8 Hz, CH=CHCOOR); mass spectrum, m/e 402 (M$^+$), 204, 202, 200, 198, 149 (base). Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.70; H, 9.45.

Reaction of Epoxide 5. Using the general procedure with an epoxide/ylide 1:2 molar ratio, the reaction time was 50 h; products **12** and **13** were isolated by using a mixture of benzene–ether (95:5) as eluent (yields 36% and 12%, respectively). Some starting material (34%) was recovered.

Compound **12** is a colorless viscous oil (bp 165 °C (0.9 mmHg)): $[\alpha]_D$ −27.9° (c 0.44); IR ν_{max} 1720 (C=O α,β-unsaturated ester), 1650, 1170, 1155, 1110, 1060 cm^{-1}; ^{1}H NMR 2.78 (1 H, br, H-C$_2$), 3.75 (4 H, singlet, OCH$_2$CH$_2$O), 4.04 (2 H, t, J = 7 Hz, OCH_2CH$_2$CH$_2$CH$_3$), 5.64 (1 H, d, J = 16 Hz, CH=CHCOOR), 6.87 (1 H, dd, J = 16, 8 Hz, CH=CHCOOR); mass spectrum, m/e 430 (M$^+$, base), 415, 402, 386, 369, 368, 358, 357, 316, 315, 252. Anal. Calcd for $C_{27}H_{42}O_4$: C 75.31; H, 9.83. found: C, 75.37; H, 9.85.

Product **13** after crystallization from methanol had the following: mp 92–96 °C; $[\alpha]_D$ −32.0° (c 0.44); IR ν_{max} 1720 (C=O α,β-unsaturated ester), 1650, 1205, 1170, 1155, 1105, 1035 cm^{-1}; ^{1}H NMR 2.80 (1 H, br, H-C$_2$), 3.84 (4 H, s, OCH$_2$CH$_2$O), 4.12 (2 H, q, J = 7 Hz, OCH_2CH$_3$), 5.72 (1 H, d, J = 16 Hz, CH=CHCOOR), 6.97 (1 H, dd, J = 16, 7 Hz, CH=CHCOOR) (in CDCl$_3$); mass spectrum, m/e 402 (M$^+$, base), 388, 387, 358, 357, 342, 341, 340, 330, 329, 325, 317, 315, 314. Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.61; H, 9.43.

Reaction of Epoxide 6. Using the general procedure with an epoxide/ylide 1:2 molar ratio, the reaction time was 26 h; products **14** and **15** were isolated by using a mixture of benzene–ether (8:2) as eluent (yields 30% and 6%, respectively). Some starting material (6%) was recovered; other products were not identified.

Compound **14** is a colorless viscous oil (bp 130 °C (0.7 mmHg)): $[\alpha]_D$ −16.5° (c 0.92); IR ν_{max} 3620, 1720 (C=O α,β-unsaturated ester), 1650, 1150 cm^{-1}; ^{1}H NMR 2.75 (1 H, br, H-C$_2$), 4.13 (2 H, t, J = 6 Hz, OCH_2CH$_2$CH$_2$CH$_3$), 5.75 (1 H, d with splitting, J = 15 Hz, CH=CHCOOR), 7.03 (1 H, dd, J = 15, 8 Hz, CH=CHCOOR); mass spectrum, m/e 402 (M$^+$), 384, 374, 370, 369, 297, 295, 280, 149 (base). Anal. Calcd for $C_{26}H_{42}O_3$: C, 77.56; H, 10.52. Found: C, 77.59; H, 10.49.

Compound **15** is a colorless viscous oil (bp 120 °C (0.7 mmHg)): $[\alpha]_D$ −14.0° (c 0.27); IR ν_{max} 3620, 1720 (C=O α,β-unsaturated ester), 1650, 1150 cm^{-1}; ^{1}H NMR 2.75 (1 H, br, H-C$_2$), 4.20 (2 H, q, J = 7 OCH_2CH$_2$), 5.75 (1 H, d with splitting, J = 15 Hz, CH=CHCOOR), 7.05 (1 H, dd, J = 15, 8 Hz, CH=CHCOOR); mass spectrum, m/e 374 (M$^+$), 358, 356, 342, 341, 317, 316, 304, 301, 300, 286, 279, 148 (base). Anal. Calcd for $C_{24}H_{38}O_3$; C, 76.96; H, 10.23. Found: C, 76.91; H, 10.25.

Reduction of Aldehyde 9. Aldehyde **9** (50 mg) in ether (ca. 3 mL) was treated with AlLiH$_4$ (ca. 5 mg) and allowed to stand at gentle reflux for 30 min. The excess hydride was decomposed with H$_2$O. From the reaction mixture, worked up in the usual way, 2β-(hydroxymethyl)-A-norcholestane (**17**) was isolated by chromatography on silica gel, using a 7:3 benzene–ether mixture as eluent.

Compound **17**, after several crystallizations from methanol, had the following: mp 144–146 °C; $[\alpha]_D$ +28.0° (c 0.14); IR ν_{max} 3630 (OH), 1040, 1020 cm^{-1}; ^{1}H NMR 3.35 (2 H, unresolved d, CH$_2$OH); mass spectrum, m/e 388 (M$^+$), 373, 248, 234, 233 (base).

Registry No. **1**, 17343-82-7; **2**, 2789-50-6; **3**, 53755-30-9; **4**, 1753-61-3; **5**, 10429-04-6; **6**, 968-54-7; **7**, 96096-33-2; **7** (acid), 96096-34-3; **8**, 96096-35-4; **9**, 96150-04-8; **10**, 96096-36-5; **11**, 96096-37-6; **12**, 96096-38-7; **13**, 96096-39-8; **14**, 96096-40-1; **15**, 96096-41-2; *cis*-**16**, 96096-42-3; *trans*-**16**, 96096-43-4; **17**, 7044-12-4; tributyl(carbethoxymethyl)phosphonium bromide, 1834-01-1; 2β,3-epoxy-5α-androstan-17β-ol, 6958-01-6; 5α-cholest-2-ene, 570-73-0.

Synthesis of Trimethylsilyl-Substituted α-Allenic and β-Acetylenic Amines from Imines and Propargylic and Allenic Organoboranes

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The inhibitory action of certain α-allenic and β-acetylenic amines on mitochondrial monoamine oxidase (MAO), a flavin-linked enzyme which is responsible for the oxidative inactivation of the transmitter amines, has been the subject of intense interest in recent years.[1] This is due to the correlation between the inactivation of MAO and the relief of depression which has been exploited clinically. Several synthetic methods have been developed to prepare these amines.[1-3] One approach involved the use of imines to react with allenic and propargylic organometallic reagents.[3] The reactions produced β-acetylenic amines or mixtures of β-acetylenic amines and the corresponding α-allenic amines depending on the structure of imines and the nature of the organometallic reagents. We recently reported that the condensation reactions of aldehydes and ketones with propargylic organoborane intermediates derived from 1-(trimethylsilyl)-1-alkynes produced trimethylsilyl-substituted α-allenic alcohols with high regioselectivity and excellent isolated yields.[4] Our continuing interest in the chemistry of propargylic and allenic organoboranes has led us to explore their reactions with

(1) (a) Sahlberg, C.; Ross, S. B.; Fagervall, I.; Ask, A.-L.; Claesson, A. *J. Med. Chem.* **1983**, *26*, 1036–1042. (b) White, R. L.; Smith, R. A.; Krantz, A. *Biochem. Pharmacol.* **1983**, *32*, 3361–3364. (c) Krantz, A.; Lipkowitz, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4156–4159.

(2) (a) Castelhano, A. L.; Krantz, A. *J. Am. Chem. Soc.* **1984**, *106*, 1877–1879. (b) Castelhano, A. L.; Pliura, D. H.; Taylor, G. J.; Hsieh, K. C.; Krantz, A. *Ibid.* **1984**, *106*, 2734–2735. (c) Sahlberg, C.; Claesson, A. *Acta Chem. Scand., Ser. B* **1982**, *B36*, 179–185. (d) Claesson, A.; Sahlberg, C. *Tetrahedron Lett.* **1978**, 1319–1322. (e) Casara, P.; Jund, K.; Bey, P. *Ibid.* **1984**, *25*, 1891–1894.

(3) (a) Moreau, J.-L. In "The Chemistry of Ketenes, Allenes, and Related Compounds"; Patai, S., Ed.; Wiley: New York, 1980; pp 381–382 and references cited therein. (b) Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1984**, 1004–1005.

(4) Wang, K. K.; Nikam, S. S.; Ho, C. D. *J. Org. Chem.* **1983**, *48*, 5376–5377.

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