Notes

Peracid Oxidation of 3,4,5-Trialkylated Furans: A Novel Ring Expansion Reaction of 3-Methyldecahydrocyclododeca[*b*]furan

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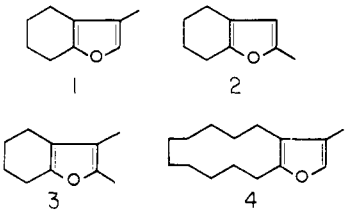
A variety of alkylated furan compounds are known to be toxic to mammals[1] with several having been shown to be metabolized by the mixed function oxidase (MFO) enzyme system to even more toxic substances.[2] Thus, it has become important to investigate the structures and characteristics of these metabolites. To this end, we have chosen a set of model compounds (structures 1–4) and

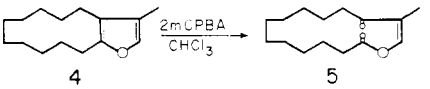


oxidized them with *m*-chloroperbenzoic acid which is regarded, by some, as a mimic of the MFO enzyme system. Even though the validity of mCPBA as a mimic remains to be verified, the oxidation results are quite interesting and useful.

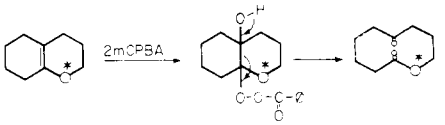
Reaction pathways for the peracid oxidations of 1–3 have been described previously[3-5] and are presented in generalized form with Figure 1. It is important for understanding this article to point out that when R_1 = H and R_2 = CH_3, epoxide Ib and lactone Ie are formed. In contrast, when R_1 = CH_3 and R_2 = H, epoxide Ia and ester Id are formed. *Further, ester If derives from an intramolecular rearrangement of Id which is apparently not operational from lactone Ie.* This latter point is particularly germane to the discussion on the oxidation pathway for substrate 4 which is the subject of this report.

Results and Discussion

In contrast to the other members of this furan group, compound 4 reacted in what appeared to be an uncharacteristic manner (eq 1). In fact, it was analogous to a reaction presented earlier by Borowitz[6] (eq 2). Thus, reaction 1 was interesting from three points of view: (a) it was a ring expansion reaction with both high yields and preserved functionality for further elaboration; (b) it appeared to result from a Borowitz type reaction which was unique in the series; and (c) it amounted to an ozonolysis of the more substituted olefin of a 3,4,5-trialkylated furan.

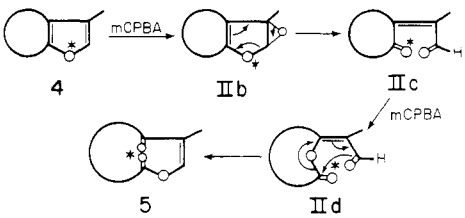


(1)



(2)

An alternative mechanism for the production of **5** is shown as an intramolecular rearrangement in eq 3. It is analogous to the rearrangement Id → If but with the large-ring analogue of lactone Ie. This alternative was particularly attractive because it not only rationalized the product formation but also followed a sequence (i.e., compare intermediates Ib and IIb) which was consistent with the other furans in this group. In order to distinguish between these two mechanistic sequences, the following hypothesis was derived. An ^{18}O label placed at the furan oxygen would give compound **5** labeled at the ester oxygen if the Borowitz mechanism was followed and at the ester carbonyl oxygen if the alternative intramolecular rearrangement mechanism was obeyed (see the asterisk in eq 2 and 3).



(3)

Compound 4 was therefore synthesized with ^{18}O incorporated in the later steps of the synthetic sequence (Scheme I). ^{18}O incorporation with the ketone D was 51% after two cycles. Subsequent synthetic steps to furan 4 were forgiving and left the level of incorporation at 50% as evidenced by NMR spectroscopy[7] and mass spectrometry. The ^{13}C isotope resonance at 137 ppm (C-2 of 4) for the carbon attached to the ^{18}O was 0.036 ppm upfield of the carbon bearing ^{16}O which is typical. Likewise, the ring juncture carbon (C-13a, 152 ppm) bearing the ^{18}O label was 0.041 ppm upfield of its ^{16}O analogue.

On oxidation with two equivalents of mCPBA at 0 °C in CH_2Cl_2, compound **5** was formed in 85% yield. NMR spectroscopy revealed that there was only *one* upfield ^{13}C–^{18}O resonance and that was for the ester carbon at 169.9 ppm. The upfield shift of 0.043 ppm is consistent with the ^{18}O label being on the carbonyl oxygen.[5] Had it been on the ester oxygen, the upfield shift to this carbon would have been 0.01 ppm.[5] The limit of detection for label in this compound is 2% on the basis of the signal to noise ratio and line-shape analysis. It is clear, then, that the intramolecular rearrangement mechanism is operating in this system as is shown in eq 3. *Thus, the oxidation of 4 is not an exception to the now established sequence*

(1) (a) Jennings, P. W.; Reeder, S. K.; Hurley, J. C.; Caughlan, C. N.; Smith, G. D. *J. Org. Chem.* **1974**, *39*, 3392. (b) Jennings, P. W.; Hurley, J. C.; Reeder, S. K.; Holian, A.; Lee, P.; Caughlan, C. N.; Larsen, R. D. *Ibid.* **1976**, *41*, 4078. (c) Jennings, P. W.; Reeder, S. K.; Hurley, J. C.; Robbins, J. E.; Holian, S. K.; Holian, A.; Lee, P.; Pribanic, J. A. S.; Hull, M. W. "Effects of Poisonous Plants on Livestock"; Academic Press: New York, 1978; pp 217–228.

(2) Holian, S. K. M. S. Thesis, Montana State University, 1975.

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(4) Gingerich, S. B.; Jennings, P. W. *J. Org. Chem.* **1983**, *48*, 2606.

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(6) (a) Borowitz, I. J.; Williams, G. J.; Gross, L.; Rapp, R. *J. Org. Chem.* **1968**, *33*, 2013. (b) Borowitz, I. J.; Gonis, G.; Kelsey, R.; Rapp, R.; Williams, G. J. *Ibid.* **1966**, *31*, 3032.

(7) Vederas, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 374.

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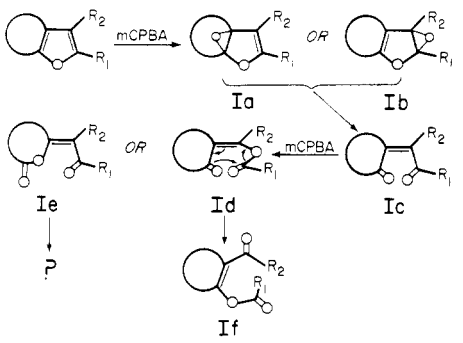
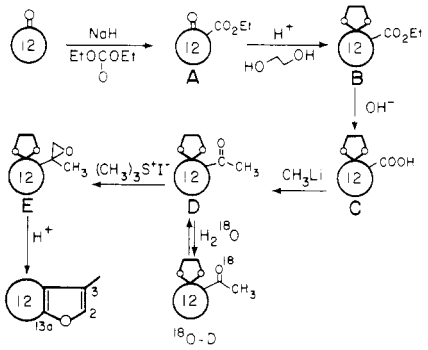


Figure 1.

Scheme I



for 3,4,5-trialkylated furans. Moreover, it must be concluded that compound Ie must be too constrained by ring size to facilitate the proper geometry for the intramolecular rearrangement.

Conclusions

Trialkylated furan compounds of substitution pattern 3,4,5 appear to follow a general mechanistic sequence: epoxidation, rearrangement to an enedione analogue, and subsequent Baeyer-Villiger oxidation. In cases where the product ester is free to rotate, the cross-ring carbonyl oxygen may react as a nucleophile to facilitate an intramolecular rearrangement. In the particular case of 3-methyl 4,5-cycloalkylated furans where a large ring is involved, the result is a high yield of ring-expanded product.

Experimental Section

General Methods. Proton and ^{13}C NMR were collected on a Bruker WM250 spectrometer using $CDCl_3$ as a solvent. Mass spectra data were collected on either a VGMM16 or a VG7070E. In the determination of ^{18}O incorporation by ^{13}C NMR spectroscopy, sweep widths of 300 Hz were typically used. Data was acquired in a 4K block and transformed as an 8K block. The $H_2{}^{18}O$ (99%) was obtained from Stohler.

Preparation of 3-Methyl-4,5,6,7,8,9,10,11,12,13-decahydrocyclododeca[*b*]furan (4). Preparation of Keto Ester A and Ketal–Ester B. To a 500-mL round-bottom flask containing petroleum ether and washed NaH (15.85 g, 50% oil dispersion, Baker) was added 300 mL of dry diethyl carbonate. The flask was flushed with N_2 for 0.5 h prior to NaH addition. A solution of cyclododecanone (30.97 g, Aldrich) in 50 mL of diethyl carbonate was then added over a 2-h period. After the addition was complete, the solution was allowed to reflux overnight, poured into an ice cold solution of 20 mL of acetic acid in 100 mL of H_2O, and then extracted five times with ether. The ether layer was washed with H_2O and brine and dried over anhydrous K_2CO_3. Removal of solvent under reduced pressure gave 40 g of yellow oil which was chromatographed on SiO_2 to give a 75% yield of ethyl 2-cyclododecanonecarboxylate (A): IR (neat) 1742, 1711 cm^{-1}; ^1H NMR ($CDCl_3$) 4.18 (2 H, q), 3.82 (1 H, dd), 1.2–2.8 (23 H, m) ppm; ^{13}C NMR 206.6, 170.0, 61.2, 57.6, 38.6, 26.9, 25.6, 25.3, 24.5, 24.3(2), 23.3, 22.6, 22.0, 14.0 ppm; mass spectrum, *m/e* (relative intensity) 254 (M^+), 209, 98 (100). Anal. (accurate mass) Calcd for $C_{15}H_{26}O_3$: 254.1875. Found: 254.1876. The keto ester A was then ketalyzed by using standard procedures to give the ketal–ester B which was distilled (bp 134.0–136.0 °C (0.2 mmHg)) to give a 85% yield of product. Characteristics for compound B are as follows: ^{13}C NMR ($CDCl_3$) 172.9 (s), 112.0 (s), 64.8 (t), 64.4 (t), 59.9 (d), 47.2 (d), 32.4 (t), 25.9 (t), 25.6 (t), 24.5 (t), 24.3 (t), 24.2 (t), 22.4 (t), 22.2 (t), 21.9 (t), 19.7 (t), 14.1 (q) ppm; mass spectra, M^+ 298; IR 1754 cm^{-1} (neat).

Preparation of Carboxylic Acid C. To a solution of ketal–ester B (11.6 g in 35 mL of THF) was added 60 mL of 5 N NaOH and the solution refluxed for 20 h. After the mixture sat in an ice bath for 2 h, the crystals that formed were filtered and washed with ether. The ether soluble crystals were identified as starting cyclododecanone. The insoluble material was acidified in EtOH, and the crystals that formed were filtered to give 4.15 g (42% yield) of 1,4-dioxaspiro[4.11]pentadecane-12-carboxylic acid (C): mp 98.5–100.0°C (benzene); IR (KBr) 2850, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) 10.5 (1 H, br s), 3.9–4.1 (4 H, m), 3.1 (1 H, dd), 1.25–2.05 (20 H, m) ppm; ^{13}C NMR 174.9, 112.9, 64.89, 64.81, 47.4, 31.6, 26.2, 26.0, 25.0 24.4, 22.6(2), 22.5, 22.2, 20.0 ppm; mass spectrum, *m/e* (relative intensity) 270 (M^+), 143, 99 (100). Anal. (accurate mass) Calcd for $C_{15}H_{26}O_4$: 270.1830. Found: 270.1833.

Preparation of Methyl Ketone D. A solution of C (2.24 g in 50 mL of dry ether) was placed in a two-neck round-bottom flask cooled to 0 °C and purged with N_2. Two equivalents of MeLi (1.55 M, Alfa) in 20 mL of ether were added dropwise to the stirred solution over a period of 2 h. The solution was stirred for an additional hour at 0 °C and then overnight at room temperature. The reaction was hydrolyzed by adding it, in small portions, to a vigorously stirred ice–water solution which was extracted several times with ether. The combined ether fractions were dried over anhydrous $MgSO_4$ and evaporated at reduced pressure to give 1.60 g (72% yield) of the desired 12-acetyl-1,4-dioxaspiro[4.11]-pentadecane (D) as a white solid (mp 85–87 °C): IR ($CHCl_3$) 1718 cm^{-1}; ^1H NMR ($CDCl_3$) 4.8–4.0 (4 H, m), 3.2 (1 H, d), 2.08 (3 H, s), 1.1–2.0 (16 H, m) ppm; ^{13}C NMR 209.7, 112.9, 64.3, 64.2, 52.8, 32.0, 31.8, 26.1, 25.7, 24.7, 23.4, 23.3, 22.4, 22.1, 22.0, 19.9 ppm; mass spectrum, *m/e* (relative intensity) 268 (M^+), 225, 141, 99 (100). Anal. (accurate mass) Calcd for $C_{16}H_{28}O_3$: 268.2039. Found: 268.2037.

Preparation of Epoxide E. To a solution of finely ground $(CH_3)_3S^+I^-$ (2.38 g in 20 mL of THF) at −15 °C was added 4.5 mL of a solution of *n*-BuLi (2.6 M ether solution, Aldrich) with stirring for 15 min. The ketal–ketone D (1.06 g in 1.5 mL of THF) was then added over a period of 10 min with stirring continued at 0 °C for 2 h and then for an additional 2 h at room temperature. The reaction mixture was then poured into water and extracted several times with ether which was separated, washed with H_2O, and dried over anhydrous K_2CO_3. Since GC analysis of the ether extract showed that 70% of the ketone still remained, the procedure was repeated two more times until no ketone was observable. Evaporation of the ether gave 700 mg of 12-(2-methyloxirane)-1,4-dioxaspirane[4.11]pentadecane (E) (65% yield) as an oil mixture of diastereomers (major isomer): ^1H NMR 3.90 (4 H, m), 2.68 (1 H, d, J = 5.7 Hz), 2.18 (1 H, d, J = 5.7 Hz), 1.27 (3 H, s), 1.2–1.9 (21 H, m) ppm; ^{13}C NMR 114.0, 64.6, 63.8, 56.7, 54.6, 45.6, 32.2, 26.8, 25.9, 24.6, 23.2, 22.8, 22.6, 22.4, 22.3, 19.9, 19.0 ppm; mass spectrum, *m/e* (relative intensity) 282 (M^+), 253 (100), 197, 155.

Preparation of Furan 4. The ketal–epoxide E was then cyclized to the furan, by treating a stirred solution of ketal epoxide (700 mg) in 25 mL of pentane with 7 mL of 5 N HCl for 2 h. The reaction mixture was then extracted several times with pentane, washed with 10% $NaHCO_3$, and dried over anhydrous K_2CO_3. Evaporation of the solvent afforded a yellow oil which was placed on SiO_2 and eluted with pentane to give 400 mg of the desired furan 4 as a colorless oil in 76% yield: IR (neat) 1550, 1475, 1140, 975, 900, 740 cm^{-1}; ^1H NMR[8] ($CDCl_3$) 7.04 (1 H, q, J = 1.5 Hz), 2.55 (2 H, m), 2.36 (2 H, m), 1.94 (3 H, d, J = 1.5 Hz), 1.2–1.8 (16 H, m) ppm; ^{13}C NMR 151.9, 137.0, 120.5, 119.5, 27.0, 26.1, 25.1, 24.7, 24.6, 24.5, 23.3, 22.6, 22.5, 20.7, 8.7 ppm; mass spectrum, *m/e* (relative intensities) 220 (M^+, 100), 105. Anal. (accurate

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mass) Calcd for $C_{15}H_{24}O$: 220.1827. Found: 220.1827.

Preparation of the ^{18}O Analogue of 4. To a solution containing ketal-ketone D (884 mg) in 2 mL of dry THF was added 1 μL of concentrated HCl and 67 mg of $H_2{}^{18}O$ (99%, Stohler). The mixture was stirred for 4 h, quenched by adding 30 mL of CH_2Cl_2, washed with 10% $NaHCO_3$ and brine, and dried over K_2CO_3. Mass spectral analysis showed only 12% ^{18}O incorporation so the procedure was repeated and allowed to stir overnight. Removal of solvent after the same workup procedure gave 788 mg (89%) of the ketone. Mass spectral analysis showed 51% ^{18}O incorporation. ^{13}C NMR analysis of the carbonyl peak at 209.7 ppm showed two lines with the upfield resonance shifted by 0.052 ppm also showing 51% incorporation.

This ketone was then treated three times with $(CH_3)_3S^+I^-$ in order to achieve an 89% yield of the diastereomeric mixture of epoxide E. Progress of this reaction was monitored by gas chromatography. High-resolution ^{13}C NMR spectroscopy on the epoxide carbons of the major diastereomer of E revealed it to have $^{13}C^{18}O$ satellites at 0.044 and 0.034 ppm upfield of the normal ^{13}C resonances at 56.3 and 54.2 ppm, respectively. Integration of these resonances indicated 50% labeling of ^{18}O still existed.

Epoxide E-^{18}O was subsequently treated with 5 N HCl, as noted above for the unlabeled substrates, to yield 4-^{18}O in 70%. Mass spectral analysis of the furan showed 50% ^{18}O incorporation. ^{13}C NMR analysis showed the peaks at 151.9 and 137.0 ppm to give two lines each. The isotope peak for the 151.9 ppm carbon was shifted 0.041 ppm upfield, while the isotope peak for the 137.0 ppm resonance was shifted 0.036 ppm.

Oxidation of Furan 4. To a stirred solution of furan 4 (100 mg) in 10 mL of CH_2Cl_2 at 0 °C was added dropwise 2 equiv of mCPBA in 5 mL of CH_2Cl_2. After being stirred for 15 min, the reaction was washed with 5% $Na_2S_2O_3$, 10% $NaHCO_3$, and brine and dried over K_2CO_3. Removal of solvent gave the keto lactone 5 in 70% yield: IR (neat) 1760, 1666, 1652 cm^{-1}; ^1H (NMR) 7.6 (1 H, s), 2.8 (2 H, m), 2.5 (2 H, m), 1.78 (3 H, s), 1.1-1.6 (16 H, m) ppm; ^{13}C NMR 202.1 (s), 169.9 (s), 138.5 (d), 120.1 (s), 43.4 (t), 34.2 (t), 29.6 (t), 27.2 (t), 26.7 (t), 26.2 (t), 26.0 (t), 25.8 (t), 24.4 (t), 22.9 (t), 14.9 (q), ppm; mass spectrum, *m/e* (relative intensity) 252 (M^+), 224, 73 (100). Anal. (accurate mass) Calcd for $C_{15}H_{24}O_3$: 252.1719. Found: 252.1749.

Oxidation of ^{18}O Analogue of 4. In an analogous experiment, the ^{18}O-labeled 4 was oxidized and separated from its reaction mixture as noted above for compound 4. Mass spectral analysis of the product showed 50% ^{18}O incorporation. A ^{13}C NMR spectrum of the product 5-^{18}O) showed two lines at 169.9 ppm with the upfield isotope resonance shifted by 0.043 ppm which corroborated the 50% ^{18}O incorporation. Similar analysis of the vinyl carbon at 138.5 ppm failed to show an isotope resonance.

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Registry No. 4, 66090-18-4; 4-^{18}O, 93943-14-7; 5, 93943-11-4; 5-^{18}O, 93943-15-8; A, 4017-60-1; B, 93943-07-8; C, 93943-08-9; D, 93943-09-0; D-^{18}O, 93943-12-5; E, 93943-10-3; E-^{18}O, 93943-13-6; MCPBA, 937-14-4; $(EtO)_2CO$, 105-58-8; $H_2{}^{18}O$, 14314-42-2; MeLi, 917-54-4; $Me_3S^+I^-$, 2181-42-2; cyclododecanone, 830-13-7.

Facile Synthesis of β-Aryl- or β-Alkenyl-β-methyl-α,β-unsaturated Carbonyl Compounds by Palladium-Catalyzed Reaction of 1,2-Dien-4-ols with Aryl or Alkenyl Halides

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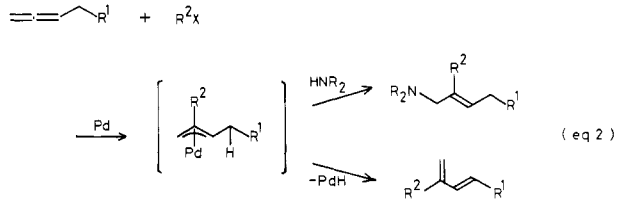
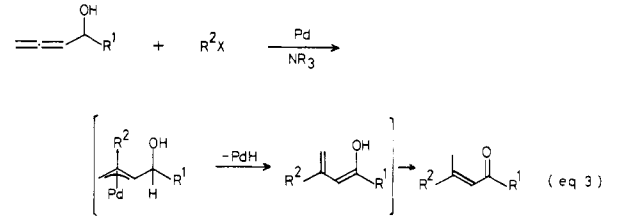
Catalytic arylation or alkenylation of olefins by way of olefin insertion to aryl- or alkenylpalladium known as the Heck reaction is a useful carbon-carbon bond forming reaction (eq 1).[1] We have found that phenyl- or alkenylpalladium complexes, formed in situ from phenyl or alkenyl halides and a Pd(0) complex, reacts with 1,2-dienes regioselectively to form (2-phenyl- or (2-alkenyl-π-allyl)-palladium intermediates which undergo amination to give 2-phenyl or 2-alkenyl allylic amines (eq 2).[2] In the reaction



of halides with 1,2-dienes in the absence of nucleophiles, 1,3-dienes are formed by β-elimination of PdH from (π-allyl)palladium complexes. In this paper, we report the facile synthesis of β-methyl-α,β-unsaturated ketones or aldehydes by palladium-catalyzed reaction of 1,2-dien-4-ols with aryl or alkenyl halides in the presence of tertiary amines (eq 3).[3]



Reaction of 2,3-butadien-1-ol (**1a**) with iodobenzene was carried out under various conditions in the presence of *N*-methylpyrrolidine or triethylamine. As shown in Table I, 3-methylcinnamaldehydes were obtained as *E/Z* mixtures in good yields by using 1,2-bis(diphenylphosphino)ethane (dppe) as a ligand of palladium in Me_2SO or CH_3CN. Dioxane and toluene are not good solvents for this reaction. 4-Phenyl- and 4-isobutyl-1,2-butadien-4-ol (**1b** or **1c**) also reacted with aryl halides at 110 °C to give the corresponding unsaturated ketones respectively.

This reaction is useful for the preparation of conjugated enones having other carbonyl groups in the same molecules, which are difficult to prepare by the well-known directed aldol condensation method.[4] The keto aldehyde **2f** was readily obtained in 61% yield by the reaction of *p*-bromobenzaldehyde with **1c** by using palladium-dppe catalyst. The aldehyde group was unaffected in this reaction. Reaction of alkenyl halide with 1 afforded conjugated dienyl carbonyl compounds in good yields. Thus, this method offers an efficient synthetic method for polyconjugated carbonyl compounds.[5]

Experimental Section

General Methods. Dioxane and toluene were distilled from benzophenone ketyl. Me_2SO was distilled from CaH_2 under reduced pressure. CH_3CN was distilled from P_2O_5. ^1H NMR spectra were taken with a Hitachi R-24A (60 MHz) or a JEOL FX-90Q (90 MHz) spectrometer. ^{13}C NMR spectra were recorded

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(3) For ketone synthesis by palladium-catalyzed reaction of allylic alcohols, see: (a) Chalk, A. J.; Magennis, S. A. *J. Org. Chem.* **1976**, *41*, 273-278. (b) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265-272. (c) Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3898-3903. (d) Kao, L.-C.; Stakem, F. G.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1982**, *47*, 1267-1277.
(4) See: Mukaiyama, T. *Org. React.* (*N.Y.*) **1982**, *28*, 203-331.
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