under reduced pressure, 250 mg of title compound showing: mp 82.5–85°; ir 3425, 2950 (sh), 2920, 2850, 1720, and 960 cm^{-1}; nmr 0.88 (br t, J = 6 Hz, 3 H, CH_3), 2.29 (t, J = 7 Hz, CH_2CO_2), 4.08 (m, 1 H, C*H*O), 5.55 ppm (m, 2 H, CH=CH); *m/e* 338. *Anal.* Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 72.04; H, 10.33.

Similarly, (±)-15-epi-11-deoxyprostaglandin E_1 was obtained from its methyl ester [mp 53–56°; ir, nmr, and mass spectra identical with that of (±)-11-deoxy-PGE_1]. *Anal.* Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 70.76; H, 10.29.

(±)-11-Deoxyprostaglandin $F_{1\alpha}$ and (±)-11-Deoxyprostaglandin $F_{1\beta}$. A solution of 500 mg of (±)-11-deoxyprostaglandin E_1 was dissolved in 30 ml of methanol and solid sodium borohydride was added portionwise until no more starting material could be detected by tlc analysis (40% ethyl acetate–60% hexane). The reaction solution was poured into water and extracted with ethyl acetate. The organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was eliminated under reduced pressure and the residue purified *via* preparative tlc to yield 303 mg of (±)-11-deoxyprostaglandin $F_{1\alpha}$ methyl ester and 98 mg of its 9β epimer. Basic hydrolysis of these compounds in the usual manner yielded (±)-11-deoxyprostaglandin $F_{1\alpha}$ [mp 97–98.5°; ir 3400 (br), 3160 (br), 2970 (sh), 2930 (s), 2860 (sh), 1695 (s), 9.75 (s) cm^{-1}; nmr 2.31 (t, J = 7 Hz, CH_2CO), 4.00–4.30 (m, 2 H, C*H*OH), 5.18–5.49 ppm (m, 2 H, *CH=CH*); *m/e* 340. *Anal.* Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.63; H, 10.85] and (±)-11-deoxyprostaglandin $F_{1\beta}$ [mp 69–70.5°; ir 3460 (br), 3250 (br), 2990 (sh), 2970 (sh), 2950 (sh), 2880 (s), 1740 (s), 990 (s) cm^{-1}; nmr 2.3 (t, J = 7 Hz, 2 H, CH_2CO), 3.78–4.1 (m, 2 H, C*H*OH), 5.24 ppm (m, 2 H, *CH=CH*); *m/e* 322 (340 − H_2O). *Anal.* Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.61; H, 10.84].

(±)-15-Epi-11-deoxyprostaglandins $F_{1\alpha}$ and $F_{1\beta}$. Similarly, title compounds were prepared from (±)-15-epi-11-deoxyprostaglandin E_1 methyl ester [mp 102–103.5°; ir 3440 (br), 2930 (s), 2855 (sh), 1700 (s), 1640 (s), and 970 (s) cm^{-1}; nmr 2.3 (t, J = 7 Hz, 2 H, CH_2CO), 4.3–4.95 (m, 2 H, C*H*OH), 5.35–5.5 ppm (m, 2 H, *CH=CH*); *m/e* as the methyl ester 336 (354 − 18). *Anal.* Calcd for $C_{20}H_{36}O_4$: C, 70.50; H, 10.66; O, 18.83. Found: C, 70.50; H, 10.72; O, 18.83] and (±)-15-epi-11-deoxy prostaglandin $F_{1\beta}$ [mp 59.0–60.5°; ir 3400 (br), 3300 (br), 2940 (s), 2860 (sh), 1690 (s), and 970 (s) cm^{-1}; nmr 2.9 (t, 2 H, J = 7 Hz, CH_2CO), 3.8–4.1 (m, 2 H, C*H*OH), 5.48 ppm (m, 2 H, *CH=CH*); *m/e* as methyl ester 336 (354 − 18). *Anal.* Calcd for $C_{20}H_{36}O_4$: C, 70.50; H, 10.66. Found: C, 70.45; H, 10.65].

(±)-9-Oxo-13-*cis*-prostenoic Acid Methyl Ester (6b). A solution of crude aldehyde **3d** (corresponding to 11.2 g of vinyl ketone **3c**) in 96 ml of dimethoxyethane was added to a previously prepared mixture of 2.98 g of 57% sodium hydride dispersion (previously washed with ether) and 30.63 g of triphenylheptylphosphonium bromide in 132 ml of dimethyl sulfoxide, dropwise at such a rate as to maintain the temperature around 25°. The reaction mixture was stirred at room temperature for 30 min after the addition was complete, and then poured into water and extracted with ethyl ether. The organic layer was washed with water and brine and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, the residue dissolved in hexane, and the solution filtered through a short column of silica gel, eluting the product with 5% ethyl acetate–95% hexane. Evaporation of the solvent gave an oil which, without further purification, was dissolved in a mixture of 50 ml of methanol and 5 ml of water. The resulting solution was treated with 4 drops of concentrated hydrochloric acid and left at room temperature for 3 hr. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent left an oily residue which was dissolved in hexane and filtered through 140 g of silica gel, eluting the product with 1% ethyl acetate–99% hexane, to yield 9.8 g of keto ester **6b** showing: ir 3000 (sh), 2920, 2845, 1655 (m), and 970 (m) cm^{-1}; nmr 0.87 (br t, 3 H, CH_3), 3.64 (s, 3 H, OCH_3), 5.24 (d of d, J = 11.0, 9.0 Hz, 1 H, H_{13}), 5.71 (d of t, J = 11.0, 7.0 Hz, 1 H, H_{14}); *m/e* 336. *Anal.* Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.68; H, 10.78.

(±)-9-Oxo-13-*cis*-prostenoic Acid (6c). A solution of 8.5 g of keto ester **6b** in 580 ml of tetrahydrofuran plus 190 ml of water was treated with 390 ml of 0.1 *N* sodium hydroxide solution for 26 hr at room temperature. The reaction solution was acidified with diluted hydrochloric acid and the product extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. Elimination of the solvent under reduced pressure gave an oil, which was filtered through 100 g of silica gel in 5% ethyl acetate–95% hexane, eluting the product with the same solvent mixture. The homogeneous fractions were combined and the solvents eliminated under reduced pressure to yield 7.7 g of **6c** exhibiting: ir 2935, 1740, and 1705 cm^{-1}; nmr 0.87 (br t, 3 H, CH_3), 5.22 (d of d, J = 11.0, 9.0 Hz, 1 H, H_{13}), 5.40 (d of t, J = 11.0, 7.0 Hz, 1 H, H_{14}). *Anal.* Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.43; H, 10.83.

Synthesis of Prostaglandin Models and Prostaglandins by Conjugate Addition of a Functionalized Organocopper Reagent[1]

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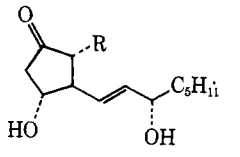
Contribution No. 406 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304. Received May 12, 1972

Abstract: Two methods are described for the preparation of an oxygen functionalized vinylcopper reagent. Reactions of this reagent with cyclic and acyclic enones give products of 1,4 addition. The labile methoxyisopropyl group was used as an alcohol protecting group for ease of formation and removal. The influence of reaction conditions such as solvents and temperature on the mode of addition and yield is discussed. (*S*)-1-Iodo-*trans*-1-octen-3-ol (**16a**) was prepared from (*S*)-1-octyn-3-ol (**17**). The optically pure iodovinylcarbinol was converted to the cuprate **2** and 1,4 addition to the hydroxy-protected cyclopentenone **14c** afforded (−)-PGE_1 (**18b**).

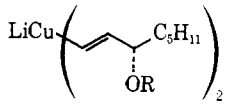
Organocopper reagents have proven to be extremely useful species in forming carbon–carbon bonds.[3] In the majority of cases these reagents have been of the unfunctionalized variety. Notable exceptions, such as an amino functionalized reagent by Corey[4] and an oxygen functionalized reagent by Eaton,[5] have recently appeared. One approach to the synthesis of E-series

(1) (a) Studies in Prostaglandins. X. (b) For part IX, see F. S. Alvarez, D. Wren, and A. Prince, *J. Amer. Chem. Soc.*, **94**, 7823 (1972).
(2) Syntex Postdoctoral Fellow, 1971–1972.
(3) For a review of conjugate addition reactions see: G. H. Posner, *Org. React.*, **19** (1972).
(4) E. J. Corey, D. E. Cane, and L. Libit, *J. Amer. Chem. Soc.*, **93** 7016 (1971).
(5) P. E. Eaton and R. H. Meuller, *ibid.*, **94**, 1014 (1972).

prostaglandins (1) would be the conjugate addition of an appropriately functionalized organocopper reagent 2 to an enone 3.[6] We now report two methods for generating the functionalized divinyl cuprate reagent and results obtained from its reaction with various α,β-unsaturated ketones to give prostaglandin models and prostaglandins.



1, $R = (CH_2)_6CO_2H$



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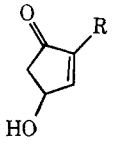
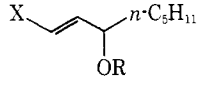


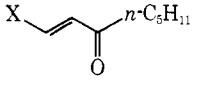
3, $R = (CH_2)_6CO_2H$

Results and Discussion

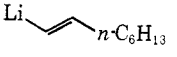
The successful formation of a divinyl cuprate reagent for the conjugate addition reaction required the generation of a vinyllithium species in high yield, and to this end a vinyl iodide was selected as the appropriate starting material. The requisite iodovinylcarbinol **4a** was prepared in two steps by conversion of 1-chloro-*trans*-1-octen-3-one (**5a**)[7] to 1-iodo-*trans*-1-octen-3-one (**5b**) with sodium iodide in acetone, and subsequent reduction with lithium aluminum hydride. Using the *O*-methoxymethylvinyl iodide **4b** as a model, the conversion to the vinyllithium **4c** was accomplished by treatment with *n*-butyllithium in hexane at *ca.* −70°. Quenching of **4c** with water gave **4d** (92%, isolated yield), and quenching with D_2O gave **4e** (d, >93%, J_{12} = 16 Hz). The choice of hexane as the solvent for the generation of the vinyllithium was essential for high yield. Use of an ether solvent such as tetrahydrofuran[8] in the halogen–metal interchange was shown after quenching with chlorotrimethylsilane to give substantial amounts of **4d** (*ca.* 30%), in addition to the silylated olefin **4f**.



4a, X = I; R = H
b, X = I; R = CH_2OCH_3
c, X = Li; R = CH_2OCH_3
d, X = H; R = CH_2OCH_3
e, X = D; R = CH_2OCH_3
f, X = $Si(CH_3)_3$; R = CH_2OCH_3



5a, X = Cl
b, X = I



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At this point, the transformation of the oxygenated vinyllithium **4c** to the copper reagent and its subsequent reaction with enones were examined. Initially we elected to convert **4c** to the cuprate with bis(triethyl phosphite)copper(I) cyanide followed by reaction with 2-cyclopenten-1-one. This choice was based on the previous observation in these laboratories by Alvarez, *et al.*,[9] that the vinyl cuprate from vinyllithium and bis(triethyl phosphite)copper(I) cyanide underwent conjugate addition in high yield, and, moreover, with the requirement of only 1 equiv of vinyllithium. Also, we knew that octenyllithium **6** was readily transformed to a divinyl cuprate in diethyl ether at −15°, and that this cuprate gave conjugate addition to various α,β-unsaturated ketones in high yields (*ca.* 80%).[10] However, when the reaction between 2-cyclopenten-1-one and the cuprate from **4c** and bis(triethyl phosphite)-copper(I) cyanide was attempted under the same conditions as were used for the vinyl case (THF solvent),[9] no 1,4 addition product was obtained. After numerous unsuccessful attempts to obtain conjugate addition, it was decided to separately examine the first phase of the overall sequence, that is, the formation of the reactive copper species.

For study of the formation of the reactive copper species, lithium reagent **4c** (in hexane) was added to a source of copper(I), and at the point when a negative Gilman test was obtained, the mixture was quenched with D_2O. While no attempt was made to rigorously evaluate the relative amounts of hydrogen abstraction and dimerization,[11] there necessarily must be a requirement for high deuterium content in the isolated olefin (**4d**) in order to have had a useful copper species for conjugate addition. Thus, this method served as a diagnostic procedure for quickly evaluating different reaction conditions. Inspection of Table I shows the

Table I. Deuterium Incorporation in Olefin **4d** after D_2O Quench of the Reaction Mixture: **4c** + Copper(I) Source

Copper(I) source	Solvent	Temp, °C	Time, min[a]	% d_1[b]
$[(EtO_3P]_2CuCN$	Et_2O	−70	15	0
CuI (0.5 equiv)	THF[c]	−20	10	10
None	Et_2O	−20	45	88
CuI	Et_2O	−20	45	82
CuI (0.5 equiv)	Et_2O	−20	45	50
$^1/_4[(Bu_3P)CuI]_4$	Et_2O	−70	45	71
None[c]	Et_2O	−20	45	85
CuI[c]	Et_2O	−20	45	76
CuI (0.5 equiv)[c]	Et_2O	−20	45	67

[a] The approximate time required to achieve a negative Gilman test. [b] Determined by mass spectrometry using the prominent peaks at *m/e* 101 and 102 ($M^+ - C_5H_{11}$). [c] *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) (1 equiv) was added to the hexane solution of **4c** to form a vinyllithium–TMEDA reagent.

bis(triethyl phosphite)copper(I) cyanide complex had completely decomposed at the point when no more active vinyllithium reagent was present (negative Gilman test). Comparison of the entries for divinyl cuprate formation from copper(I) iodide in both THF and diethyl ether shows diethyl ether to be the pre-

(6) Subsequent to the submission of this study there appeared a communication by Sih and coworkers (C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzotti, and M. Casey, *J. Amer. Chem. Soc.*, **94**, 3643 (1972)), which reported the synthesis of (−)-PGE_1 by using the reagent 2.

(7) Y. K. Yur'ev and G. B. Elyakov, *Zh. Obshch. Khim.*, **27**, 176 (1957); *Chem. Abstr.*, **51**, 12818f (1957).

(8) E. J. Corey and R. Noyori (personal communication) have independently obtained the tetrahydropyranyl ether derivative corresponding to **4a** and used this for generation of lithium and copper reagents in ether and tetrahydrofuran solvents.

(9) See ref 1b and references cited therein.

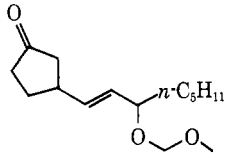
(10) J. W. Patterson, personal communication.

(11) For a detailed treatment of decomposition of vinylic copper(I) compounds, see: G. Whitesides, C. P. Casey, and J. K. Krieger, *J. Amer. Chem. Soc.*, **93**, 1379 (1971).

ferred solvent, because of decreased hydrogen abstraction which produces the olefin **4d**.

With conditions for formation of the vinylcopper species now established, we turned our attention toward conjugate addition reactions. From the standpoint of economy, reaction of a monovinylcopper seemed attractive because only 1 equiv of vinyllithium would be required. However, all attempts using the monovinylcopper reagent derived from **4c** and copper(I) iodide resulted in very low yields (*ca.* 2%) of 1,4 addition. When the divinyl cuprate (from 2 equiv of **4c** and 1 equiv of copper(I) iodide) was allowed to react with 2-cyclopenten-1-one, **7** was obtained in a yield of 12% along with a 5% yield of the 1,2-addition product **8**. This reaction was modified to include a coordinating ligand *N,N,N′,N′*-tetramethylethylenediamine (TMEDA). After generation of the vinyllithium **4c**, 1 equiv of TMEDA was added to the hexane solution to generate a vinyllithium–TMEDA reagent. Addition of this reagent to copper(I) iodide in ether led to the formation of a divinyl cuprate reagent (see Table I), which when treated with 2-cyclopenten-1-one afforded **7**[12] in approximately 80% yield, without the accompanying formation of the 1,2-adduct **8**.

During the investigation of various ligands which would promote cuprate formation, we found that addition of 2 equiv of **4c** to 1 equiv of bis(trimethyl phosphite)copper(I) iodide in diethyl ether at −50° afforded a cuprate which underwent conjugate addition to 2-cyclopenten-1-one in comparable yield to the TMEDA case. The use of the phosphite as a solubilizing ligand allowed for cuprate formation at a lower temperature, −50° *vs.* −15° using TMEDA, and offered the advantage of somewhat greater reproducibility.



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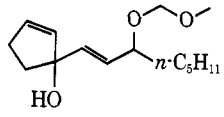

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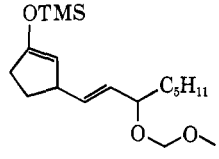
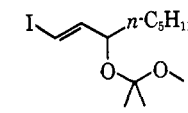
Having found conditions and complexing agents that clearly provided vinylcopper species, we turned our attention to the incorporation of a highly labile hydroxyl protecting group which was expected to be necessary for subsequent prostaglandin synthesis.[13] Alcohol **4a** was converted to **9** (*ca.* 100%) by treatment with isopropenyl methyl ether[14] and a trace of phosphorus oxychloride. Reaction of **9** with *n*-butyllithium in hexane gave the vinyllithium reagent which when treated with bis(trimethyl phosphite)copper(I) iodide gave the cuprate **10**. Reaction with several enones followed by mild hydrolysis (20% acetic acid

(12) The intermediate enolate could be trapped as the highly labile trimethylsilylated enol ether by treatment of the reaction mixture with chlorotrimethylsilane: mass spectrum (70 eV) 326 (M^+), 281 ($M - CH_2OCH_3$), 255 ($M - C_5H_{11}$).



(13) E. J. Corey, *Proc. Robert A. Welch Found. Conf. Chem. Res.*, *1968*, **12**, 51 (1969).

(14) G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50**, 1158 (1967).



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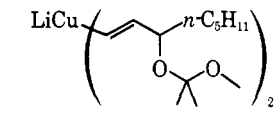

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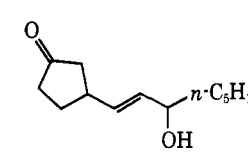
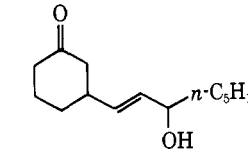


11



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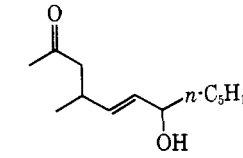
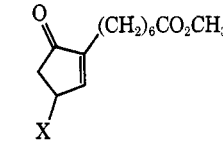


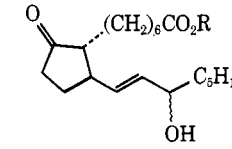
13

for 10 min at room temperature) afforded the corresponding 1,4 adducts. Thus, equivalent quantities of the divinyl cuprate and 2-cyclopenten-1-one afforded **11** (44%)[15] (see Experimental Section for spectral properties); 2-cyclohexen-1-one gave **12** (51%);[15] *trans*-3-penten-2-one gave **13** (31%).[15]

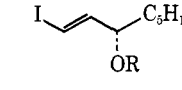
In order to apply this reaction to the preparation of a simple prostaglandin, the alkylated cyclopentenone **14a**[9] was treated with the cuprate **10**. After acid hydrolysis, a mixture of the (*dl*)-15α- and 15β-11-deoxyprostaglandin methyl esters **15a** was obtained (27% yield, 15α:15β 45:55). Chromatographic separation of these esters followed by hydrolysis with KOH in methanol gave the corresponding acids **15b** which were indistinguishable from the independently prepared compounds[9] by their tlc behavior and mixture melting points.



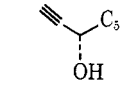
14a, X = H
b, X = OH
c, X = $OC(CH_3)_2OCH_3$



15a, R = CH_3
b, R = H



16a, R = H
b, R = $C(CH_3)_2OCH_3$



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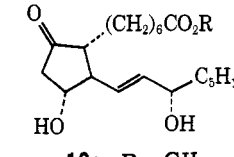
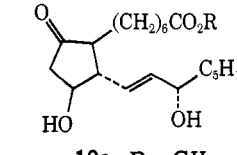


18a, R = CH_3
b, R = H



19a, R = CH_3
b, R = H

At this point it was of interest to prepare the cuprate reagent with the *S* configuration (**2**). The (*S*)-

(15) We were unable to resolve diastereomers by silica gel tlc or by glpc.

iodovinylcarbinol **16a** was prepared in 42% yield through a five-step sequence starting with (*S*)-1-octyn-3-ol (**17**).[16] Acetylenic carbinol **17** was converted to the THP derivative, which was hydroborated with 1 equiv of disiamylborane[17] in diglyme. The resulting organoborane was oxidized with 2 equiv of trimethylamine oxide[18] and this product was treated with iodine and sodium hydroxide[19] to give the THP–iodovinylcarbinol. Hydrolysis of the THP afforded (*S*)-1-iodo-*trans*-1-octen-3-ol (**16a**), $[\alpha]_D$ −4.2° (*c* 0.73, diethyl ether), +10.0° (*c* 2.76, methanol), which was identical with the racemic material by silica gel tlc and glpc. Alternatively, compound **16a** of the same optical purity was obtained through recrystallization of the diastereomeric salts obtained from the hemiphthalate of 1-iodo-*trans*-1-octen-3-ol and (−)-α-methylbenzylamine and subsequent hydrolysis.

The hydroxyenone **14b**[9,20] was converted to the *O*-methoxyisopropyl derivative **14c** by treatment with isopropenyl methyl ether and a trace of phosphorus oxychloride. The enone **14c** was allowed to react without purification with the cuprate reagent **2** derived from **16b**. The reaction mixture was poured into 20% aqueous acetic acid and the desired esters **18a** and **19a** were isolated by chromatography. The ester mixture thus obtained (1% with 80% recovery of **14b**) gave two spots by silica gel tlc. The lower R_f component was indistinguishable from (−)-15α-PGE_1 methyl ester and the higher R_f component was indistinguishable from (±)-15β-PGE_1 methyl ester by silica gel tlc with several solvent systems. The mass spectrum of the ester mixture was the same as that from (−)-15α-PGE_1 methyl ester. The above sequence when carried out with the racemic reagent **10** gave the (±) esters and in similar yields.

The esters **18a** and **19a** were separated by preparative silica gel tlc and were converted through enzymatic hydrolysis with crude pancreatic lipase to the acids **18b** and **19b**, which were isolated by preparative tlc. The isolated (−)-15α-PGE_1 (**18b**), mp 113.5–114.5°, $[\alpha]_D$ −47° (*c* 0.064, tetrahydrofuran),[21] was indistinguishable from authentic (−)-15α-PGE_1 by silica gel tlc with several solvent systems, by mixture melting point, and by mass spectrometry. The retro-15-epi-PGE_1 (**19b**) was indistinguishable from (±)-15β-PGE_1 by silica gel tlc with several solvent systems, and exhibited a positive $[\alpha]_D$ in THF; however, the quantity obtained was too small to permit further characterization.

(16) J. Fried, C. H. Lin, M. M. Mehra, and P. Dalven, *Ann. N. Y. Acad. Sci.*, **180**, 38 (1971).

(17) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 1241 (1961).

(18) *Cf.* G. Zweifel, N. L. Polston, and C. C. Whitney, *ibid.*, **90**, 6243 (1968), for the use of trimethylamine oxide in an analogous case. Without oxidation the above sequence fails due to rearrangement of the organoborane.

(19) H. C. Brown, M. W. Rathke, and M. M. Rogic, *ibid.*, **90**, 5035 (1968).

(20) An alternative preparation of **14b** (40% overall yield) consists of allylic bromination of **14a** with *N*-bromosuccinimide and subsequent treatment of the crude brominated products with silver perchlorate in 50% aqueous acetone. We thank Dr. Michael Marx for suggesting these solvolytic conditions.

(21) We have observed the $[\alpha]_D$ of (−)-15α-PGE_1 to be concentration dependent in THF. A plot of $[\alpha]_D$ *vs.* log *c* afforded an apparent linear correlation over a range of concentrations from 0.2 to 10 mg/ml. We have bracketed our value with values from several different samples of (−)-15α-PGE_1.

Experimental Section[22]

***trans*-1-Iodo-1-octen-3-ol (4a).** To a 1-l. flask equipped with magnetic stirrer and reflux condenser were added 93.1 g of *trans*-1-chloro-1-octen-3-one (**5a**)[7] (0.58 mol) and a solution of 123 g of sodium iodide (0.82 mol) in 500 ml of acetone. The mixture was heated at reflux for 3 hr, cooled to room temperature, and filtered. The solution was concentrated to *ca.* 250 ml on a rotary evaporator, poured into 500 ml of water, and extracted with three 150-ml portions of diethyl ether. The combined ether fractions were washed with 200 ml of water and 200 ml of saturated sodium sulfate solution, and dried over anhydrous sodium sulfate. Removal of ether afforded 137 g of crude *trans*-1-iodo-1-octen-3-one (**5b**), 93%. To a 1-l., three-necked flask, equipped with reflux condenser, mechanical stirrer, dropping funnel, and gas inlet tube were added 300 ml of diethyl ether and 10 g of lithium aluminum hydride (0.26 mol). The contents were maintained under nitrogen and a solution of 137 g (0.54 mol) of **5b** was added over 20 min. The mixture was heated at reflux for 1 hr, after which time the contents were cooled to room temperature followed by sequential dropwise addition of 10 ml of water, 10 ml of 15% sodium hydroxide solution, and 30 ml of water. The mixture was filtered and the filter cake was washed with two 50-ml portions of diethyl ether. Removal of the ether gave a crude product to which 300 ml of benzene was added. The water was removed by azeotropic distillation of 200 ml of benzene. Further concentration *in vacuo* afforded 123 g (89%) of *trans*-1-iodo-1-octen-3-ol (**4a**). Further purification by silica gel chromatography using 10% (v/v) diethyl ether–hexane gave an analytical sample: nmr δ 3.52 (s, 1, OH), 3.97 (m, 1, H_3), 6.15 (d, 1, J_{12} = 14.5 Hz, H_1), 6.49 (d of d, 1, J_{21} = 14.5 Hz, J_{23} = 5 Hz, H_2); ir (CCl_4) 3620, 2490 (OH), 1605 (C=C), 940 (trans CH=CH) cm^{-1}. *Anal.* Calcd for $C_8H_{15}IO$: C, 37.81; H, 5.95. Found: C, 37.78; H, 6.05.

***trans*-1-Iodo-3-methoxymethoxy-1-octene (4b).** To a 1-l. three-necked flask, equipped with mechanical stirrer, reflux condenser, dropping funnel, and gas inlet tube, was added 5.05 g of a 56% mineral oil dispersion of sodium hydride (2.83 g = 0.118 mol). The contents were maintained under nitrogen. The mineral oil was removed by washing with two 100-ml portions of pentane. After decantation of the pentane, 125 ml of anhydrous tetrahydrofuran (THF) was added, followed by a solution of 25.4 g of **4a** in 125 ml of THF. The mixture was heated at reflux for 1 hr. After cooling to room temperature, a solution of 9 g (0.11 mol) of chloromethyl methyl ether in 30 ml of THF was added dropwise over 15 min and the resulting mixture was heated at reflux for 1 hr. After cooling, the resulting mixture was poured into 500 ml of water and extracted with three 100-ml portions of diethyl ether. Removal of ether gave 29.5 g of crude product, which was chromatographed over 1 kg of silica gel with a gradient of 5–20% (v/v) diethyl ether–hexane. By this procedure, a total of 23.8 g of **4b** (80%), bp 84–85° (0.26 mm), was obtained: nmr δ 3.3 (s, 3, CH_3O), 3.9 (m, 1, H_3), 4.52 (d of d, 2, OCH_2O), 6.23 (m, 2, H_1 and H_2); ir (film) 1605 (C=C), 975, 955 cm^{-1}. *Anal.* Calcd for $C_{10}H_{19}IO_2$: C, 40.28; H, 6.42. Found: C, 40.28; H, 6.58.

***trans*-1-Iodo-3-(2′-methoxyprop-2′-oxy)-1-octene (9).** To a flask were added 5 g (19.7 mmol) of *trans*-1-iodo-1-octen-3-ol and 6 g of methyl isopropenyl ether. A trace of phosphorus oxychloride in a capillary was introduced and the flask was stoppered and set aside at room temperature for 1 hr. Analysis by tlc showed no starting alcohol present. Two drops of triethylamine were added and the mixture was concentrated in vacuum affording 6.44 g of **9** (*ca.* 100%), which was used without further purification: nmr δ 1.3 (s, 6, $(CH_3)_2C$), 3.14 (s, 3, CH_3O), 4.08 (m, 1, H_3), 6.13 (d, 1, J_{12} = 15 Hz, H_1), 6.53 (d of d, 1, J_{21} = 15 Hz, J_{23} = 6 Hz, H_2); mass spectrum (70 eV) *m/e* 311 (M − 15), 237 (M − 89).

(*S*)-*trans*-1-Iodo-1-octen-3-ol (16a). A. Synthetic Route. A mixture of 2.05 g (16.3 mmol) of (*S*)-1-octyn-3-ol (**17**),[16] 15 g of freshly distilled dihydropyran, and 1 drop of phosphorus oxychloride was set aside at room temperature in a tightly stoppered flask overnight. Three drops of triethylamine were added and the mixture was concentrated *in vacuo*. The residue was chromato-

(22) Infrared spectra were recorded with a Perkin-Elmer 237B grating spectrometer. Nmr spectra were obtained with Varian A-60 and HA-100 instruments in deuteriochloroform (*ca.* 10% v/v) with TMS, internal standard. A Perkin-Elmer 141 polarimeter was used for rotation measurements. Combustion analyses were performed by A. Bernhardt, Mulheim (Ruhr), West Germany, and by our microanalytical laboratory. We gratefully acknowledge Mr. V. Hayashida, Mr. B. Amos, Dr. M. Maddox, Mrs. J. Nelson, and Miss L. Jaime for their assistance with analytical measurements.

graphed on 120 g of silica gel with 5% (v/v) diethyl ether–hexane yielding 2.84 g (83%) of (*S*)-3-(tetrahydropyranyl-2′-oxy)-1-octyne, $[\alpha]_D$ −49.2° (*c* 1.39, Et_2O). A 100-ml flask, equipped with magnetic stirrer, reflux condenser, and gas inlet tube, was flushed with argon and charged with 20 ml of 0.56 *M* disiamylborane in diglyme.[17] The solution was cooled to *ca.* 0° and (*S*)-3-(tetrahydropyranyl-2′-oxy)-1-octyne, 2.38 g (11.3 mmol), was added. The mixture was allowed to reach room temperature and after 1.5-hr analysis by vpc showed complete disappearance of the starting acetylene. The mixture was brought to *ca.* 0° whereupon 3 g (40 mmol) of trimethylamine oxide was added in small portions over 15 min. The cooling bath was removed and the mixture was stirred at room temperature for 30 min. The mixture was poured with stirring into 100 ml of 15% sodium hydroxide solution and a solution of 8 g of iodine in 20 ml of THF was added immediately. After 30 min the layers were separated and the aqueous layer was extracted with two 50-ml portions of diethyl ether. The combined organic phases were washed with 50 ml of 5% sodium thiosulfate solution and 50 ml of saturated sodium sulfate solution. Removal of solvent and chromatography from 120 g of silica gel with 7.5% (v/v) diethyl ether–hexane afforded 2.4 g (63%) of (*S*)-*trans*-1-iodo-3-(tetrahydropyranyl-2′-oxy)-1-octene, $[\alpha]_D$ −64.4 (*c* 0.87, Et_2O). The THP was hydrolyzed in 10 ml of 60% dichloroacetic acid at room temperature for 1 hr. This mixture was poured into 50 ml of 15% sodium hydroxide solution and extracted with three 30-ml portions of diethyl ether. The combined ether fractions were washed with saturated sodium sulfate solution and concentrated. The residue was chromatographed from 120 g of silica gel with a gradient of 10–20% (v/v) diethyl ether–hexane, affording 1.44 g (80%) of (*S*)-*trans*-1-iodo-1-octen-3-ol (**16a**), $[\alpha]_D$ −4.2° (*c* 0.73, Et_2O), +10.0° (*c* 2.76, CH_3OH).

B. Resolution Method. A 1-l. three-necked flask, equipped with reflux condenser, magnetic stirrer, dropping funnel, and gas inlet tube, was flushed with nitrogen. A 57% mineral oil dispersion of 11.1 g (0.264 mol) of sodium hydride was added to the flask and washed with two 100-ml portions of pentane. After decantation of the pentane, 100 ml of benzene, 200 ml of DMF, and 38.7 g (0.261 mol) of phthalic anhydride were added. A solution of 66.7 g (0.262 mol) of *trans*-1-iodo-1-octen-3-ol (**4a**) in 100 ml of benzene was added over 30 min. The mixture was heated at 50° for 2 hr, cooled to room temperature, and poured into 1 l. of ice water. Fifty milliliters of 15% sodium hydroxide solution was added and the solution was extracted with two 200-ml portions of hexane. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with four 200-ml portions of diethyl ether. The combined ether fractions were washed with 200 ml of saturated sodium sulfate solution and concentrated to give 107 g of the crude hemiphthalate. The residue was taken up in 300 ml of methylene chloride and to this solution was added 31.7 g (0.262 mol) of (−)-α-methylbenzylamine (Aldrich). Removal of the methylene chloride afforded a mixture of diastereomeric salts which was repeatedly recrystallized from acetonitrile affording (17.4 g) the pure salt, mp 133–135°, $[\alpha]_D$ −15.7° (*c* 2.0, CH_3OH). This salt was added to 200 ml of 15% sodium hydroxide solution and the mixture was heated on a steam bath for 2 hr. After cooling, the mixture was extracted with three 50-ml portions of ether. The combined ether fractions were washed with two 50-ml portions of 4 *N* HCl and 50 ml of saturated sodium sulfate solution. Removal of ether left a residue which was chromatographed from 150 g of silica gel with 15% (v/v) diethyl ether–hexane, yielding 6.5 g of (*S*)-*trans*-1-iodo-1-octen-3-ol (**16a**), $[\alpha]_D$ +10.2° (*c* 2.59, CH_3OH).

Preparation of the Vinyllithium Reagent 4c. To a 25-ml flask equipped with magnetic stirrer and gas inlet tube were added 3.03 g (10.1 mmol) of *trans*-1-iodo-3-methoxymethoxy-1-octene and 10 ml of hexane. The contents were maintained under argon and cooled to *ca.* −70° with a Dry Ice–methanol bath. A hexane solution of *n*-butyllithium (6.8 ml of 1.5 *M* = 10.2 mmol) was added with a syringe. The solution was maintained at *ca.* −70° for 30 min. To this solution was added 1 ml of D_2O and the contents were warmed to room temperature with stirring. The layers were separated and the hexane was removed *in vacuo*. The residue was chromatographed on 140 g of silica gel with a gradient of 2–20% (v/v) diethyl ether–hexane giving 1.56 g (90%) of 3-(methoxymethoxy)-1-octene-*1-d*: nmr δ 3.3 (s, 3, CH_3O), 3.92 (m, 1, Hz), 4.53 (d of d, 2, J = 6.5 Hz, OCH_2O), 5.05 (d, 1, J_{12} = 16 Hz, H_1), 5.62 (d of d, 1, J_{21} = 16 Hz, J_{23} = 7 Hz, H_2); mass spectrum (70 eV) *m/e* 102 (100), 101 (5).

Conjugate Addition Reactions. Method A. *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA) (1 equiv) was added to the vinyllithium reagent in hexane at −70°. After 30 min this mixture was transferred to 0.5 equiv of copper(I) iodide in a volume of diethyl ether five times that of the hexane solution at −70°. The temperature of this mixture was allowed to rise to *ca.* −15° and held there until a negative Gilman test was obtained (*ca.* 20 min). The temperature of the mixture was brought to *ca.* −70° and 0.5 equiv of enone (relative to vinyl iodide) was added. After 1 hr, the reaction mixture was worked up by pouring into 10% aqueous ammonia and isolating the product of 1,4 addition by chromatography on silica gel. For example, from **4b** was obtained **7**: nmr (CCl_4) δ 3.24 (s, 3, CH_3O), 3.81 (m, 1, >C*H*O), 4.43 (d of d, 2, J = 7.8 Hz, OCH_2O), 5.24 (d of d, 1, J_{trans} = 15 Hz, J_{vic} = 7 Hz, olefinic H), 5.60 (d of d, 1, J_{trans} = 15 Hz, J_{vic} = 6 Hz, olefinic H); ir (CCl_4) 1740 (C=O), 972 (trans CH=CH) cm^{-1}; mass spectrum (70 eV) *m/e* 45 (100), 183 (17, M − C_5H_{11}). *Anal.* Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 71.19; H, 10.48.

Method B. The hexane solution containing 1 equiv of the vinyllithium at *ca.* −70° (no TMEDA) was transferred to 0.5 equiv of bis(trimethyl phosphite)copper(I) iodide in a volume of diethyl ether five times that of the hexane solution at *ca.* −70°. The temperature was brought to *ca.* −50° and held there until a negative Gilman test was obtained (*ca.* 20 min). The temperature was lowered to *ca.* −70° and the enone was added. After 1 hr, the reaction was worked up by pouring into 20% acetic acid. The product was isolated by chromatography. Reaction of **10**, with 2-cyclopenten-1-one, afforded **11**: nmr δ 5.6 (m, 2, olefinic protons); ir (film) 3350 (OH), 1735 (C=O), 972 (trans CH=CH) cm^{-1}; mass spectrum (70 eV) *m/e* 139 (M − C_5H_{11}). *Anal.* Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.62; H, 10.79.

Reaction of **10** with cyclohexenone afforded **12**: nmr δ 5.5 (m, 2, olefinic protons); ir (film) 3350 (OH), 1710 (C=O), 972 (trans CH=CH) cm^{-1}; mass spectrum (70 eV) *m/e* 153 (M − C_5H_{11}). *Anal.* Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.81; H, 10.86.

Reaction of **10** with *trans*-3-penten-2-one afforded **13**: nmr δ 5.5 (m, 2, olefinic protons); ir (film) 3350 (OH), 1710 (C=O), 972 (trans CH=CH) cm^{-1}; mass spectrum (70 eV) *m/e* 194 (M − H_2O). *Anal.* Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.14; H, 11.51.

Synthesis of (−)-PGE1. To a flask were added 0.21 g (0.875 mmol) of **14b**, 3 ml of methyl isopropenyl ether, and a small drop of phosphorus oxychloride. The flask was stoppered and after 30 min, analysis by tlc showed complete conversion to **14c**. Two drops of triethylamine were added and the mixture was concentrated *in vacuo* to give **14c**, which was used without further purification. To a 25-ml flask equipped with magnetic stirrer and gas inlet tube were added 0.554 g (1.7 mmol) of **16b** and 5 ml of hexane. The contents were maintained under argon and cooled to *ca.* −70°. A hexane solution of *n*-butyllithium (1.2 ml of 1.5 *M* = 1.8 mmol) was added and the solution was stirred at −78° for 30 min. To a 50-ml flask equipped with alcohol thermometer, magnetic stirrer, gas inlet tube, and rubber serum cap were added 0.395 g (0.9 mmol) of bis(trimethyl phosphite)copper(I) iodide and 25 ml of diethyl ether. The contents were maintained under argon and cooled to *ca.* −70°. The hexane solution of vinyllithium reagent was added with a syringe. The contents were warmed to *ca.* −50°, held there for 30 min (Gilman test negative), and then cooled to *ca.* −70°. A solution of **14c** from above in 2 ml of diethyl ether was added at once. The resulting mixture was stirred at *ca.* −70° for 1 hr, then poured into 100 ml of 20% acetic acid. After stirring for 20 min at room temperature, the ether layer was separated and the aqueous layer was extracted with 30 ml of diethyl ether. The ether layers were combined, washed with 20 ml of saturated sodium sulfate, and concentrated. The residue was chromatographed from 100 g of silica gel (deactivated with 2 ml of formic acid), using a gradient of 40–80% (v/v) ethyl acetate–hexane. From the earlier fractions 0.17 g of **14b** was recovered. A total of 8 mg of a crude mixture of **18a** and **19a** was obtained. This mixture (by tlc **18a** and **19a** appear to be present in equal amounts) was chromatographed by preparative tlc with ethyl acetate. This afforded 3.2 mg (1%) of **18a** and 0.9 mg of **19b**. For enzymatic hydrolysis 1.0 g of crude hog pancreas lipase (Sigma) was stirred at *ca.* 0° for 1 hr with 10 ml of salt solution (0.1 *M* NaCl, 0.05 *M* $CaCl_2$). This slurry was centrifuged at 10,000*g* for 30 min. The supernatant liquid was adjusted to pH 7 with 0.1 *N* sodium hydroxide and was divided into equal portions which were used to hydrolyze the PG esters. Thus, **18a** was placed in a small flask equipped with a magnetic stirrer. The lipase solution was added and the mixture was sonicated to disperse the ester. After 5 min the ester was completely hydrolyzed as judged by tlc. The mixture was poured into 50 ml of acetone and the resulting mixture was filtered through Celite. The solution was concen-

trated to *ca.* 5 ml on a rotary evaporator and the residue was extracted with two 5-ml portions of ethyl acetate. The combined ethyl acetate fractions were concentrated and the residue was purified by preparative tlc, affording 2.4 mg of crude **18b**, which was recrystallized twice from ethyl acetate–hexane: white needles, mp 113.5–114.5° (undepressed by admixture with authentic (−)-PGE_1), $[\alpha]D$ −46.9° (*c* 0.064, THF). Hydrolysis of **19a** by the same method gave **19b** (*ca.* 0.3 mg, oil).

Acknowledgments. We thank Dr. Francisco S. Alvarez, Mr. Douglas Wren, and Mr. Anthony Prince for generous supplies of the enone **14a**, and reference samples of (±)-PGE_1, 15-epi-(±)-PGE_1, and (±)15α- and 15β-desoxyprostaglandins, and Dr. John W. Young for assistance with the enzymatic hydrolysis.

Thermodynamically Unstable Enols. 2-Methyl-2-penten-3-ols from 4-Isopropylidene-5,5-dimethyl-2-dimethylamino-1,3-dioxolane

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Contribution from William Ramsay and Ralph Forster Laboratories, University College, London, England. *Received March 15, 1972*

Abstract: By treating 4-isopropylidene-5,5-dimethyl-2-dimethylamino-1,3-dioxolane (**1**) with acidic compounds ranging from *tert*-butyl alcohol to acetic acid, a series of simple aliphatic enols has been generated in high concentrations (0.45 to >1 *M*). The enols so obtained proved to be kinetically surprisingly stable and their formation as well as rearrangement into the corresponding ketones was followed by nmr over periods of 15 min up to 20 days at room temperature. On contact with D_2O all enols could be converted smoothly into the deuterioenols which, in general, were more stable than the ordinary enols, an exception being the dideuterioxy derivative **6-D**, the lability of which was comparable to that of **6**. The lifetime of the enols could be extended by using polar aprotic solvents such as dimethylformamide and, in particular, dimethyl sulfoxide. The facile generation and successful stabilization of the enols are attributed to (i) the reactivity of the heterocycle **1**, which contains a preformed ammonium enolate system, (ii) the use of mild acids including methanol which liberates the enol in a slow reaction such that acidity is never allowed to build up, not even locally, the reaction being homogeneous throughout, and (iii) the nature of the solvent.

We have shown recently that 4-isopropylidene-5,5-dimethyl-2-dimethylamino-1,3-dioxolane (**1**) is a highly reactive heterocycle,[1] which on treatment with catalytic amounts of benzoic acid gave a simple aliphatic enol, namely 2,4-dimethyl-1,3-pentadien-3-ol (**2**). Depending on the experimental conditions the enol **2** could be observed for periods up to 10 days at room temperature before it had rearranged irreversibly into the isomeric ketone **3**.[2]

The question remained whether the enol **2** owed its metastable character merely to the mild and carefully controlled conditions of its genesis or whether the conjugation of two double bonds, worth about 3.5 kcal/mol,[3] also came into play. Accordingly, we sought to generate a nonconjugated enol and it occurred to us that the reaction of heterocycle **1** with suitably weak acids other than benzoic acid[2] might allow the transient formation of such an enol.

Results

Reaction of 1 with Alcohols. Heterocycle **1**, either neat or as a 1.1 *M* solution in dimethylformamide (DMF) or CCl_4, remained unchanged at room temperature, provided it had been purified rigorously and stored in the absence of traces of acid, moisture, oxygen, and ultraviolet light. However, on contact with alcohols, water, carboxylic acids, and their deuterated analogs **1** broke up readily and a variety of enols could be generated and observed spectroscopically (Scheme I). For example, after *ca.* 2 molar equiv (100% excess) of methanol had been added to a 1.1 *M* solution of **1** in spectrograde CCl_4 at 27°, the 100-MHz nmr spectrum in Figure 1a could be scanned after a few minutes. When the same reaction was carried out with less methanol (1.25 molar equiv), the enol **4** had reached its maximum concentration (>0.8 *M*) after *ca.* 30 min; in addition to the enol **4** *ca.* 15% of the dienol **2** was obtained in these conditions. An even greater amount of pentadienol **2** (*ca.* 25%) was formed when using an equimolar quantity of methanol (*cf.* Figure 1b).

(1) (a) H. M. R. Hoffmann, K. E. Clemens, E. A. Schmidt, and R. H. Smithers, *J. Amer. Chem. Soc.*, **94**, 3201 (1972); (b) E. A. Schmidt, Ph.D. Thesis, to be submitted in 1972.

(2) H. M. R. Hoffmann and E. A. Schmidt, *J. Amer. Chem. Soc.*, **94**, 1373 (1972).

(3) Calculated from the heat of hydrogenation of 1-butene (30.3 kcal/mol) and that of 1,3-butadiene (57.1 kcal/mol): see J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, New York, N. Y., 1964.

(4) Enols **4**, **4-D**, and **6** have been formulated with weak intramolecular hydrogen bonds in solvent CCl_4. Ideally, such a formulation should be supported by high dilution ir data. However, such measurements have proved uninformative, since, *e.g.*, the α-methoxyenol **4** is accompanied by either pentadienol **2** or methanol (*cf.* below). Furthermore, dimethylformamide is also present in at least equimolar quantity and competes as a hydrogen bond acceptor. In any event it seems clear that intramolecular hydrogen bonding cannot be important in DMSO[5] and pure DMF solutions. We thank a referee for comments on this question.

(5) For recent references see, *e.g.*, O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964); F. A. L. Anet, L. M. Sweeting, T. A. Whitney, and D. J. Cram, *Tetrahedron Lett.*, 2617 (1968); W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, **90**, 6250 (1968); G. Satzinger, *Tetrahedron*, **27**, 3739 (1971).