Prostaglandins and Congeners. 18. Synthesis of Cyclopentenolone Precursors to Prostaglandins from 2,5-Dihydro-2,5-dimethoxyfurans

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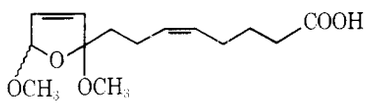
Received October 21, 1977

A synthesis of cyclopentenolone **1**, a useful prostaglandin precursor, from 2,5-dihydro-2,5-dimethoxyfuran (DHDMF) intermediates is described. A sequential hydrolysis–aldol cyclization under mildly acidic conditions was found to be a useful procedure for conversion of DHDMF derivatives such as **2** to cyclopentenolones with the pattern of functionality exemplified by **4**. The latter compound was isomerized in dilute sulfuric acid to **1**. The preparation of the requisite precursors to **1** and some of its derivatives are discussed.

Several synthetic schemes for the preparation of cyclopentenolone **1** have been reported.[2] We wish to report a six-stage synthesis of this useful prostaglandin precursor from readily available materials which proceeds in an overall yield of ca. 20%.

The method is dependent on the previously observed rearrangement of cyclopentenolones of type **4** to the thermodynamically favored isomer of type **1**.[3] Since **4** was in principle the product of aldol cyclization of *cis*-enedione **3**, we sought a synthesis of the latter compound or a suitable derivative. It was found that 2,5-dihydro-2,5-dimethoxyfuran **2** fulfilled this synthetic objective and that these dihydrofuran (DHDMF) derivatives[4] represent useful general precursors to cyclopentenolones.[5]



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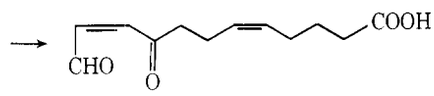

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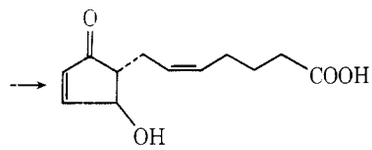

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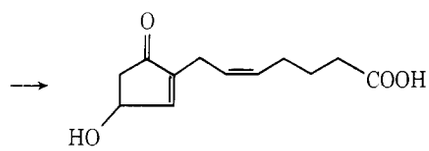
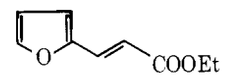


1

Hydrogenation of ethyl β-(2-furyl)acrylate (**5**) using Raney nickel in ethanol afforded the propionate **6** in 90–95% yield if ammonium hydroxide was added to suppress ring reduction. Oxidative methoxylation[4] of **6** with bromine in methanol gave in ca. 85% yield the dihydrofuran **7** which contains the desired latent functionality. Treatment of **7** with diisobutylaluminum hydride in toluene at −75 °C followed by careful neutral workup and distillation gave the aldehyde **8** in 91% yield. Condensation of **8** with ylid salt **9**[6] in dimethyl sulfoxide (Me_2SO) gave the required **2** in 80–85% yield.

Our attempts to convert **2** to *cis*-enedione **3** were only partly successful, since in all cases the corresponding *trans*-enedione was also formed and the isolation was inconvenient.[7] It was decided therefore to combine the hydrolysis of the DHDMF



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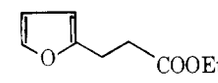

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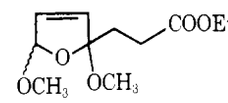

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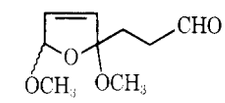

8

$Ph_3P{=}CH(CH_2)_3COONa$

9

function with the aldol cyclization step in a one-pot procedure. After evaluation of several buffer systems including chloroacetate, formate, and acetate, it was found that the weakly acidic (pH ca. 5.5–6.5) system derived from 0.1 M **2**, 0.2 M NaH_2PO_4, and 0.1 M Na_2HPO_4 in boiling aqueous dioxane resulted in the desired sequential conversion to **3** and **4**. While formation of the trans isomer of **3** was not suppressed, the desired **4** was formed in ca. 50–55% yield.

Since the isomerization represented by the conversion of **4** to **1** may be a consequence of hydration–dehydration, we examined the feasibility of equilibration under acid catalysis. Control experiments demonstrated that the desired conversion occurred cleanly in ca. 1 N H_2SO_4 in aqueous dioxane at reflux temperature. This finding allowed a further simplifying modification in our scheme. When the conversion (**2** → **3** → **4**) is complete, as demonstrated by chromatographic (TLC) and spectral (NMR) examination of an aliquot, the solution containing crude **4** may be treated with sulfuric acid and the sequence to give the desired **1** may be completed. This procedure has routinely resulted in a one-pot conversion of **2** to **1** in an overall yield of 45–55%, after appropriate workup and chromatography.

Work in these laboratories has shown that the bis(trimethylsilyl) [$(Me_3Si)_2$] derivative **12** is a useful blocked precursor to prostaglandins via the conjugate addition reaction with organocuprate reagents.[8] When crude **1** obtained from the above sequence was subjected to silylation by a mixture of hexamethyldisilazine and chlorotrimethylsilane in pyridine, the resulting **12** was obtained directly in 45–55% overall yield from **2** by simple Kugelrohr distillation in excellent purity. The sequence reported here therefore has the advantage of requiring no chromatographic purification.

Since we were interested in the introduction of other groups than hydroxy on the cyclopentenone ring, acid-catalyzed equilibration of **1** in methanol was examined. After reaction in methanolic sulfuric acid (1 N) for a period of time somewhat greater than that required for the concomitant Fisher esterification, the ether **13** was produced cleanly in 78% yield.

For preparation of the methyl ester **14** of cyclopentenolone **1**, the following modification proved useful. The crude reac-

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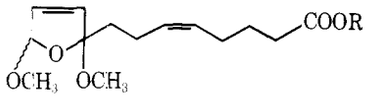
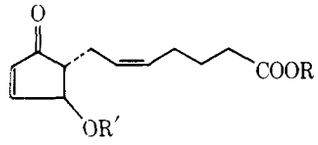
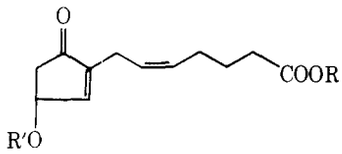
tion mixture containing the sodium salt of **2** in Me_2SO was treated with excess iodomethane at room temperature to give



2, R = H
10, R = Me



4, R = R′ = H
11, R = Me; R′ = Me_3Si



1, R = R′ = H
12, R = R′ = Me_3Si
13, R = R′ = Me
14, R = Me; R′ = H

10 in 82% yield (from **8**). A system which employed 0.1 M **10**, 0.1 M NaH_2PO_4, and 0.03 M sodium acetate in 2:1 dioxane–water at reflux temperature served to convert **10** to **11** in 45% yield after silylation and distillation. Removal of the Me_3Si function and subsequent isomerization using the chloral–triethylamine system provides **14**.[2d]

Experimental Section

Boiling points are uncorrected. NMR spectra were recorded at 100 MHz on a Varian HA-100 spectrometer in deuteriochloroform solution with chemical shifts reported in δ units downfield from internal tetramethylsilane. Mass spectra were recorded on an AEI MS-9 mass spectrometer. Elemental compositions were determined at resolution $M.\Delta M$ = 10 000 by the peak matching method using perfluorokerosene as the standard. For TLC on silica gel plates, two systems were employed: 30:20:1 heptane–ethyl acetate–acetate acid (system A) and 100:1 ethyl acetate–acetic acid (system B). Spots were visualized with 2,4-dinitrophenylhydrazine spray.

Hydrogenation of 5. A solution of 21.6 g (0.13 mol) of **5**[9] in 260 mL of ethanol and 8.75 mL (0.13 mol) of concentrated ammonium hydroxide was hydrogenated on a Parr shaker in the presence of 3 mL of catalyst (No. 28 Raney active nickel washed with water to neutrality and then with ethanol). When hydrogen uptake ceased (ca. 8 h; 105% of theory for 1 mol uptake) the catalyst was filtered and washed with ethanol.

Solutions from two such runs were combined and concentrated in the presence of toluene chaser. The residue was distilled to give 42.8 g (89%) of propionate **6** as a colorless liquid, bp 87–88.5 °C (8 mm) (lit.[9] bp 94–95 °C (10 mm)).

Dimethoxy Ester 7. To a mechanically stirred solution of 42.5 g (252 mmol) of furano ester **6** in 750 mL of methanol at −25 °C was added 53 g (500 mmol) of sodium carbonate. To the stirred mixture was added a solution of 40.5 g (253 mmol) of bromine in 250 mL of methanol during 2.5 h at −25 to −22 °C. Decolorization was rapid throughout the addition, after which the stirred mixture was brought to 25 °C during 10 min and maintained at that temperature for 20 min to ensure solvolysis of intermediate bromo compounds. The mixture was filtered, and the filtrate was partitioned with brine and ether. The ether extract was washed with brine and dried over magnesium sulfate. Evaporation and distillation through a 6 in. Vigreux column gave 48.9 g (84%) of light yellow liquid, bp 78–84 °C (0.2 mm): NMR δ 3.10, 3.18, 3.44, and 3.49 (methoxy singlets for two diastereomers), 4.12 (q, 2, CH_2O), 5.44 and 5.72 (broad s, 1, OC**H**O for each of two diastereomers); MS 229.1069 [calcd for $C_{11}H_{17}O_5$ (M − H), 229.1075].

Dimethoxyaldehyde 8. To a mechanically stirred solution of 48.9 g (212 mmol) of ester **7** in 800 mL of toluene was added 263 mL of 0.89 M diisobutylaluminum hydride in toluene during 90 min at −75 °C. After stirring an additional 30 min at −75 °C, the solution was treated dropwise with 5 mL of methanol during 10 min. While maintaining the above cooling, the solution was treated with 100 mL of water during 15 min, warmed to 0 °C during 15 min, and stirred at 0–5 °C for 15 min (ice bath; hydrolysis is exothermic at this stage). The mixture was saturated with sodium sulfate and filtered through Celite with the aid of ethyl acetate. The organic phase of the filtrate was separated, washed successively with water and brine, dried briefly over magnesium sulfate, and filtered. The filtrate was treated with ca. 0.1 mL of pyridine and ca. 15 mg of hydroquinone and concentrated.

The residue was short-path distilled to give 35.87 g (91%) of light yellow liquid: bp 76–78 °C (0.25 mm, bath 110 °C); NMR δ 3.12, 3.20, 3.46, and 3.51 (methoxy singlets for two diastereomers), 5.40 and 5.75 (broad s, 1, OC**H**O for two diastereomers), and 9.73 (m, 1, C**H**O); MS 185.0804 [calcd for $C_9H_{13}O_4$ (M − H), 185.0814].

Dimethoxy Acid 2. A stirred suspension of sodium hydride [prepared by washing 18.5 g (440 mmol) of 57% dispersion free of mineral oil with 3 × 120 mL of petroleum ether] in 220 mL of dry Me_2SO was heated to 65 °C while monitoring hydrogen evolution and maintained at that temperature for 45 min. The cloudy, light-grey solution was cooled to 17 °C and treated during 15 min with a solution of 98 g (221 mmol) of 4-carboxybutyltriphenylphosphonium bromide in 370 mL of Me_2SO while cooling at 20–25 °C. The red solution was stirred for 15 min at 25 °C, cooled to 17 °C, and treated during 20 min with a solution of 35.8 g (192 mmol) of aldehyde **8** in 150 mL of Me_2SO, while cooling at 17–20 °C. After the addition the solution was stirred at 20–23 °C for 60 min. The solution was concentrated by distillation of Me_2SO under high vacuum (bath 55°), and the resulting residue was treated with 800 mL of water and 2.3 g (22 mmol) of sodium carbonate. The mixture (pH ca. 11) was extracted with ethyl acetate to remove triphenylphosphine oxide.

The aqueous phase was carefully acidified to pH 6 by addition of a 4 M NaH_2PO_4 solution, saturated with sodium chloride, and extracted with 4 × 500 mL of 3:2 ether–petroleum ether. The combined extracts were filtered, washed with brine, dried over magnesium sulfate briefly, filtered, and concentrated to give 43.6 g (85%) of light amber oil. TLC (system A): two green spots, R_f 0.45 and 0.41, for product epimers; NMR δ 3.14, 3.21, 3.48, and 3.52 (methoxy singlets for two epimers), and 5.4 (m, 2, *cis*-C**H**=C**H**); MS 270.1456 (calcd for $C_{14}H_{22}O_5$, 270.1467).

Dimethoxy Ester 10. The dimethoxyaldehyde **8** (49.3 g, 264 mmol) was submitted to the above Wittig reaction with the appropriate scale of materials. After completion of the 60-min reaction period, the solution containing the crude sodium salt of **2** was treated during 10 min with 112 g (790 mmol) of iodomethane while cooling at 30–35 °C. The solution was stirred at room temperature for 18 h and the bulk of the Me_2SO and excess iodomethane were removed in vacuo. The resulting sludge was treated with 700 mL of water. The product was extracted from the mixture of solid triphenylphosphine oxide and solution into several portions of petroleum ether. The extract was washed successively with saturated $NaHCO_3$, water, and brine and dried over potassium carbonate. After concentration to ca. 250 mL, the extract was cooled to 5 °C and filtered. The filtrate was concentrated to give 61.5 g (82%) of light orange liquid: NMR δ 3.11, 3.20, 3.45, and 3.51 (methoxy acetal singlets for two epimers), and 3.66 (methyl ester). Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.58; H, 8.45.

Cyclopentenolone 4. To a stirred solution of 2.70 g (10 mmol) of dimethoxy acid **2** and ca. 10 mg of hydroquinone in 25 mL of peroxide-free 3:2 (v/v) dioxane–water was added 25 mL of phosphate buffer (0.4 M NaH_2PO_4, 0.2 M Na_2HPO_4). After heating to reflux temperature during 20 min, the solution was maintained at that temperature until reaction was complete according to the criteria below. To follow the course of reaction, 2-mL aliquots were withdrawn and partitioned with EtOAc–brine. The EtOAc phase was evaporated and spotted for TLC (System A); when reaction was complete, spots for **2** were absent. Also absent was a green spot, R_f 0.30, corresponding to *cis*-enedione **3**. The indicated products were the *trans*-enedione corresponding to **3** (orange spot, R_f 0.35) and cyclopentenolone **4** (light orange spot, R_f 0.13). The NMR spectra of aliquots were also useful in observing the conversion.[10]

After 90 min at reflux, the solution was cooled, saturated with sodium chloride, acidified with 3 mL of 4 N HCl, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated. The residue was subjected to dry column chromatography on Woelm Act. III silica gel with System B to afford 1.09 g (49%) of amber oil: NMR δ 4.70 (broad s, 1, C**H**OH), 6.11 (d of d, 1, COC**H**=C), and 7.55 (d of d, 1, COC=C**H**). In addition the spectrum showed resonances due to 5–10% of cyclopentenolone **1** (see below).

Cyclopentenolone Trimethylsilyl Ether 11. A stirred solution of 5.69 g (20 mmol) of dimethoxy ester **10**, 2.65 g (19.2 mmol) of $NaH_2PO_4 \cdot H_2O$, 525 mg (6.4 mmol) of anhydrous sodium acetate, and 20 mg of hydroquinone in 135 mL of peroxide-free dioxane and 68 mL of water was heated at reflux temperature for 27 h. The solution was cooled, saturated with sodium chloride, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated.

To a stirred solution of the residue (5.0 g) in 20 mL of pyridine at 0 °C was added 5.0 mL (ca. 24 mmol) of hexamethyldisilazane, followed during 2 min by 2.5 mL (ca. 20 mmol) of chlorotrimethylsilane. The mixture was stirred at ambient temperature for 3 h. Volatile matter was removed in vacuo (bath 30 °C), and the resulting residue was slurried with dry petroluem ether. After filtration, the filtrate (ca. 200 mL) was concentrated to 50 mL and filtered. The filtrate was concentrated, and the residue was distilled on a Kugelrohr apparatus (0.02 mm, air bath 130 °C) to give 2.80 g (45%) of light yellow liquid: NMR δ 0.18 (s, 9, trimethylsilyl ether), 3.65 (s, 3, CH_3OOC), 4.70 (broad s, 1, CHO), 6.25 (dd, 1, COCH=C), 7.51 (dd, 1, COC=CH). Anal. Calcd for $C_{16}H_{26}SiO_4$: C, 61.90; H, 8.44. Found: C, 61.67; H, 8.52.

Telescoped Procedure. Preparation of Cyclopentenolone 1. To a mechanically stirred, refluxing mixture of 1300 mL of peroxide-free 3:2 (v/v) dioxane–water and 1300 mL of phosphate buffer [prepared by dissolving 138 g (1.00 mol) of $NaH_2PO_4 \cdot H_2O$ and 70.9 g (0.50 mol) of Na_2HPO_4 in water and diluting to 2500 mL] was added 100 mg of hydroquinone, followed by dropwise addition of neat dimethoxy acid **2**(70.4 g, 260 mmol) during 2 h. After an additional 45-min reflux period the hydrolysis–cyclization was complete by the criteria above for the preparation of cyclopentenolone **4.**

The stirred solution was cooled to 50 °C and treated dropwise with 170 mL (ca. 312 g, 3.12 mol) of concentrated H_2SO_4 during 10 min. The dark solution was stirred at 65 °C for 18 h. The NMR spectrum of an aliquot worked up as below showed the conversion of **4** to **1** to be complete. The solution was cooled, saturated with sodium chloride, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated to give 68 g of dark oil.

A 64-g portion of the crude was dissolved in 50 mL of 100:5:2 $CHCl_3$–THF–HOAc and subjected to chromatography on 1250 g of Davison No. 923 silica gel (deactivated with 5% water). Elution was carried out with chloroform progressively enriched in THF to ratio 100:14:2 $CHCl_3$–THF–HOAc, followed by ether, followed by ether progressively enriched in acetone (to 10%). Fractions which contained cyclopentenolone **1** (R_f 0.45 on TLC with system B) were combined to give 12.1 g (21%) of one-spot material and 22.0 g (38%) of material with minor contamination. With the above TLC system, isomer **4** (R_f 0.47) is not effectively separated from **1.**

Cyclopentenolone **1:** NMR δ 2.95 (m, doubly allylic CH_2), 4.95 (m, 1, CHOH), 5.56 (broad t, *cis*-CH=CH), and 7.20 (broad s, CO-C=CH).

Other chromatography systems are probably as good or better than the above (cf. purification of **4**). The conditions above for rearrangement of **4** to **1** are ca. 2 N sulfuric acid. An equally effective procedure is to make the reaction solution ca. 1 N in sulfuric acid and carry out the rearrangement at reflux temperature for 16–24 h.

$(Me_3Si)_2$ Derivative 12. To a stirred solution of 76 g of crude **1** [prepared as described above from 82.0 g (440 mmol) of aldehyde **8**] in 625 mL of pyridine at 10 °C was added 124 mL (ca. 900 mmol) of hexamethyldisilazane followed by 105 mL (ca. 900 mmol) of chlorotrimethylsilane. The mixture was stirred at ambient temperature for 3 h. The volatile matter was evaporated under vacuum (bath 40 °C), and the resulting residue was slurried with 300 mL of hexane, treated with charcoal, and filtered. The filtrate was concentrated to give 101 g of dark oil, which was distilled on a Kugelrohr apparatus (0.03 mm, air bath 155 °C) to give 55.2 g of light amber liquid (36% overall yield from aldehyde **8**): NMR δ 0.18 (s, 9, trimethylsilyl ether), 0.28 (s, 9, trimethylsilyl ester), 4.93 (m, 1, CHO), 7.16 (m, 1, COC=CH). Anal. Calcd for $C_{18}H_{32}Si_2O_4$: C, 58.65; H, 8.75. Found: C, 58.89; H, 8.69.

Methyl Ether–Methyl Ester 13. To a stirred solution of 6.28 g (27.8 mmol) of hydroxy acid **1** in 280 mL of methanol was added 7.6 mL (ca. 140 mmol) of concentrated H_2SO_4. The solution was stirred under reflux for 40 h, at which point the resonance at δ 4.95 in **1** was completely replaced by a resonance at 4.48 in the NMR spectrum of a worked up aliquot. The solution was cooled, treated cautiously with 7.4 g (70 mmol) of sodium carbonate, and concentrated. The residue was partitioned with ether and brine. The ether phase was washed with brine, dried over magnesium sulfate, and concentrated. The residue was short-path distilled to give 5.45 g (78%) of light yellow liquid: bp 130–134 °C (0.05 mm); NMR δ 3.41 (methyl ether), 3.66 (methyl ester), and 4.48 (m, 1, CHO). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.28; H, 8.38.

Acknowledgments. The author wishes to thank his colleagues in this work W. A. Hallett, I. Jones, J. Nocera, and K. J. Sax for certain large-scale preparations; E. R. Ruso for the catalytic hydrogenation studies; L. Brancone and associates for microanalytical data; W. Fulmor, G. Morton, and associates for spectral data; and R. T. Hargreaves and associates for mass spectral data.

Registry No.—**1,** 52419-12-2; *cis*-**2,** 65377-96-0; *trans*-**2,** 65377-97-1; *trans*-**3,** 65338-45-6; **4,** 65377-98-2; **5,** 623-20-1; **6,** 10031-90-0; *cis*-**7,** 65338-46-7; *trans*-**7,** 65338-47-8; *cis*-**8,** 65338-48-9; *trans*-**8,** 65338-49-0; *cis*-**10,** 65338-50-3; *trans*-**10,** 65377-99-3; **11,** 65338-51-4; **12,** 62555-09-3; **13,** 65378-00-9; 4-carboxybutyltriphenylphosphonium bromide, 17814-85-6.

References and Notes

(1) For paper 17 of this series, see E. L. Tolman, R. Partridge, and E. T. Barris, *Prostaglandins*, **14,** 11 (1977).
(2) (a) M. B. Floyd, *Synth. Commun.*, **4,** 317 (1974); (b) C. J. Sih, J. B. Heather, R. Sood, P. Price, G. Peruzzotti, L. F. H. Lee, and S. S. Lee, *J. Am. Chem. Soc.*, **97,** 865 (1975); (c) G. Stork, C. Kowalski, and G. Garcia, *ibid.*, **97,** 3258 (1975); (d) M. Kobayashi, S. Kurozumi, T. Toru, and S. Ishimoto, *Chem. Lett.*, 1341 (1977).
(3) Isomerizations of this general type have been carried out with: (a) aqueous sodium carbonate, ref 2a and ref 5 (see below); (b) triethylamine-chloral, ref 2c; (c) alumina, G. Piancatelli and A. Scettri, *Tetrahedron Lett.*, 1131 (1977).
(4) For a review, see N. Elming, *Adv. Org. Chem.*, **2,** 67 (1960).
(5) After this work was completed, a report on the use of DHDMF compounds as precursors to cyclopentenolones appeared: T. Shono, Y. Matsumura, H. Hamaguchi, and K. Nakamura, *Chem. Lett.*, 1249 (1976).
(6) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91,** 5675 (1969).
(7) For studies of the conversion of DHDMF compounds to enediones, see: (a) ref 5; (b) J. Levisalles, *Bull. Soc. Chim. Fr.*, 997 (1957).
(8) W. A. Hallett, A. Wissner, C. V. Grudzinskas, and M. J. Weiss, *Chem. Lett.*, 51 (1977).
(9) I. F. Bel'skii, N. I. Shuikin, and V. M. Shostakovskii, *Dokl. Akad. Nauk SSSR*, **152,** 862 (1963).
(10) For pertinent NMR data for enediones such as **3** and its trans isomer respectively, see: (a) ref 5; (b) J. P. Ward and D. A. VanDorp, *Recl. Trav. Chim. Pays-Bas*, **88,** 989 (1969).