(21) M. Kitadani, A. Yoshikoski, Y. Kitahara, J. Campello, J. D. McChesney, D. J. Watts, and E. Wenkert, *Chem. Pharm. Bull.*, **18**, 407 (1970), have reported the preparation of this compound by the lithium aluminum hydride reduction of 18-tosyloxyabieta-8,11,13-triene; however, in our hands this reduction failed. Hydrocarbon **23** was prepared by Wolff–Kishner reduction of the aldehyde derived from dehydroabietic acid by a modification of the procedure described in ref 8.
(22) V. J. Traynelis and W. L. Hergenrother, *J. Org. Chem.*, **27**, 2377 (1962).
(23) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **80**, 211 (1958).
(24) Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were taken as films or potassium bromide pellets on a Perkin-Elmer Model 137 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60 spectrometer using deuteriochloroform as a solvent and tetramethylsilane as an internal standard. Signals are reported in parts per million relative to this standard (δ). Optical rotatory dispersion and circular dichroism measurements were made in methanol using a Jasco ORD/UV-5 spectropolarimeter. Glc data were obtained using an F and M Model 810 chromatograph with a 10 ft × 0.125 in. OV-17 on Chromosorb W column at a temperature of 260°. Mass spectra were determined using a Du Pont 21-4'0 mass spectrometer at 70 eV ionization potential. Unless otherwise noted, all compounds were homogeneous by tlc and/or glc.
(25) For this and all compounds in this series the isopropyl group appears as a doublet, J = 6–7 Hz, at δ 1.20 ± 0.05. H-15 is a multiplet centered in the region of δ 2.80.
(26) This compound was unstable, and satisfactory analyical data could not be obtained.
(27) J. W. Huffman and P. G. Arapakos, *J. Org. Chem.*, **30**, 1604 (1965).
(28) R. A. Benkeser and E. M. Kaiser, *J. Org. Chem.*, **29**, 955 (1964).

Synthesis of Prostaglandins by Conjugate Addition and Alkylation of a Directed Enolate Ion. 11-Deoxyprostaglandins[1]

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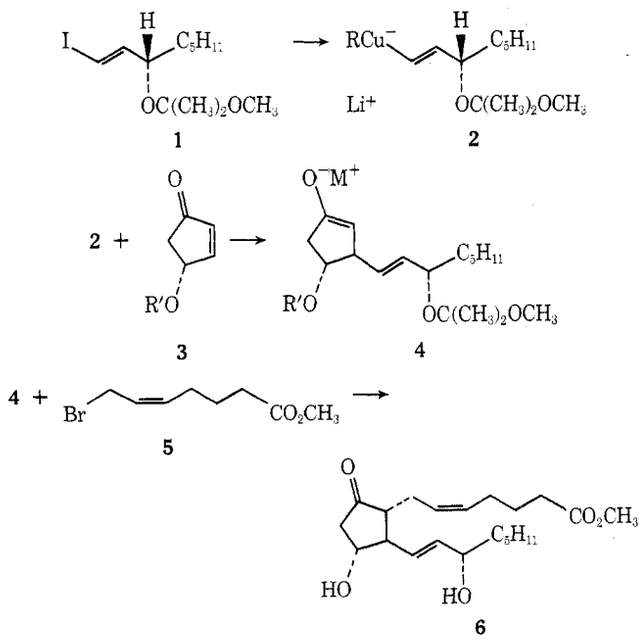
Bis[*trans*-3-(2'-methoxy-2'-prop-2'-oxy)-1-octenyl]copper lithium (**2**) has been added to cyclopent-2-enone and the resultant enolate ion converted to the silyl enol ether **8**. This silyl enol ether was then alkylated with methyl *cis*-7-bromooct-5-enoate to yield 11-deoxyprostaglandin E_2 methyl ester (**10**). By similar reactions (±)-5,6-dehydro-11-deoxyprostaglandin E_2 and (±)-11,15-deoxyprostaglandin E_2 methyl esters (**15** and **20**) were prepared.

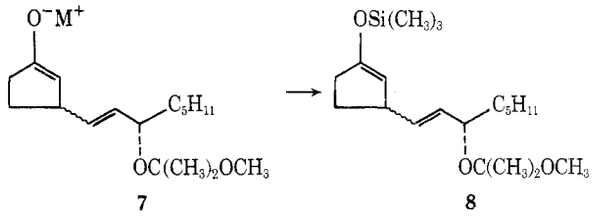
Conjugate addition of an organocopper reagent followed by alkylation of the resulting nonequilibrated enolate ion is a convenient method for converting α,β-unsaturated ketones to vicinally dialkylated ketones.[2,3] The use of the cuprate derived from 3-(*S*)-*trans*-1-iodo-1-octen-3-ol in prostaglandin synthesis *via* conjugate addition to 2-alkylated cyclopentenones has been actively investigated in these laboratories[4] and elsewhere.[5] With the goal of developing a short and converging synthesis of prostaglandins, we were interested in employing this conjugate addition in conjunction with an alkylation of the resultant enolate ion (**4**) to a protected 4-hydroxycyclopent-2-enone, *e.g.*, **3**, in



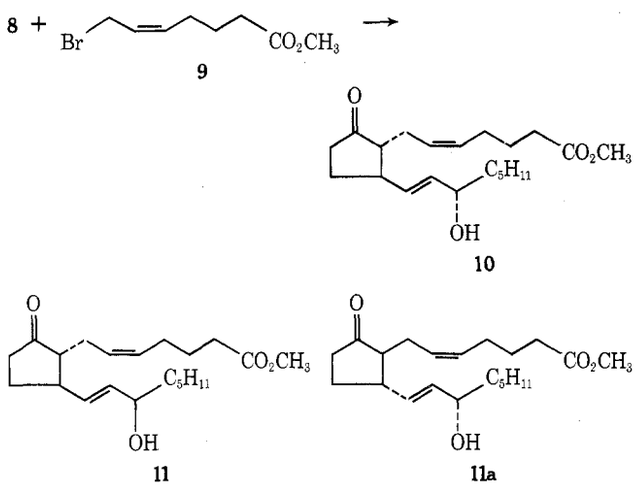
order to introduce both functionalized side chains characteristic of these natural products. Based on steric considerations, we expected that such an approach would give prostaglandins, incorporating mainly the trans,trans stereochemical relationship at carbons 8, 11, and 12, while the use of the cuprate **2** obtained from 3-(*S*)-*trans*-1-iodo-1-octen-3-ol methoxy isopropyl ether (**1**)[4] would establish the natural α configuration at C-15. Thus the prostaglandins resulting from such a sequence of reactions would be predominantly a mixture of PGE_2 (**6**) and 8,11,12-*epi*-PGE_2.[6]

We wish to describe here the application of this method to the synthesis of several 11-deoxyprostaglandins.

11-Deoxyprostaglandin E_2 (10).[7] Our initial attempts to alkylate enolate ion **7** obtained from the addition of achiral cuprate **2** (R = *trans*-CH=CHCH[OC-$(CH_3)_2OCH_3$]C_5H_{11}[4]), to cyclopent-2-enone were unsuccessful under a variety of conditions. Consequently, we turned to the expedient of trapping the enolate ion as the trimethylsilyl ether (**8**). This intermediate was not sufficiently stable for characterization or extensive purification. However, extraction of the trimethyl phosphite–copper iodide complex from a hexane solution of **8** with DMSO gave silyl ether **8** of adequate purity for the alkylation step.



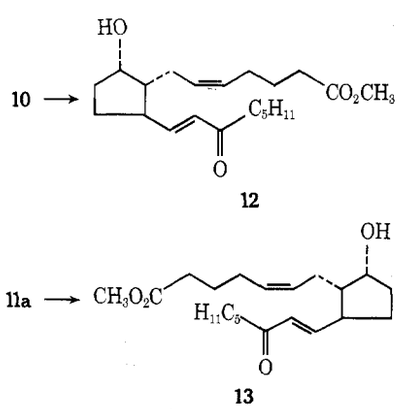
In the alkylation procedure employed here, the achiral lithium enolate **7** (M = Li) was generated in liquid ammonia by reaction of silyl ether **8** with lithium amide. An excess of the alkylating agent, methyl *cis*-7-bromo-5-heptenoate (**9**), was added and, after a suitable period at −35°, the reaction was quenched with ammonium chloride. Aqueous acetic acid removed the methoxy isopropyl ether group, resulting in a mixture of (±)-11-deoxy-PGE_2 and (±)-11-deoxy-15-*epi*-PGE_2 methyl esters (**10** and **11**). By use of a fourfold ratio of allylic bromide to enolate ion



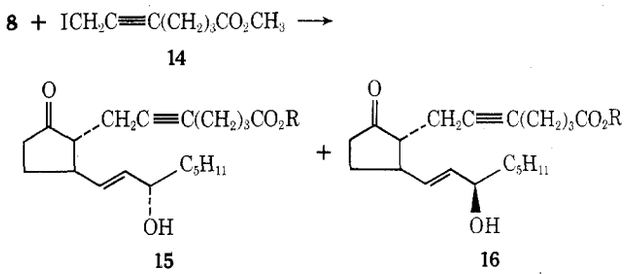
and a 3-min reaction period, we have been able to isolate the racemic monoalkylation products **10** and **11**, essentially free of polyalkylated materials.[8] An overall yield of 47% for this sequence of reactions consisting of cuprate addition, enolate trapping and regeneration, and alkylation has been obtained.

In a similar process, utilizing chiral cuprate **2** (R = 1-pentynyl),[9] we have also prepared optically active PGE_2 methyl ester. Thus the chiral enolate ion obtained from cyclopenten-2-one and the mixed cuprate reagent **2** (R = 1-pentynyl) was trapped with trimethylsilyl chloride to yield the chiral enol ethers **8**. The copper pentyne was removed from the crude product by precipitation from cold hexane and the silyl enol ether was then alkylated as described above to yield a mixture of 11-deoxy-PGE_2 and 11-deoxy-8,12-*epi*-PGE_2 methyl esters (**10** and **11a**) in 40% yield.

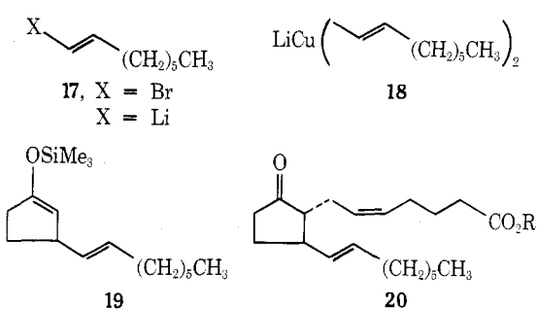
The proof of structure for compound **10** is based on spectral and chromatographic identity with 11-deoxy-PGE_2 which was prepared independently from PGA_2 isolated from *Plexaura homomalla via* reduction of the 10,11 double bond with zinc in acetic acid–methanol.[10] The fact that product **11a** differs from 11-deoxy-PGE_2 methyl ester only with respect to the absolute stereochemistry of carbons 8 and 12 was established by reduction of **10** and **11a** with potassium tri-*sec*-butylborohydride to the 9α alcohols followed by oxidation of the 15-hydroxyl groups with DDQ to yield hydroxy enones **12** and **13**. Compounds **12** and **13** were identical except for possessing mirror-image ORD spectra.



(±)-5,6-Dehydro-11-deoxyprostaglandin E_2 (15, R = H). In addition to 11-deoxy-PGE_2, we have also prepared (±)-5,6-dehydro-11-deoxy-PGE_2 (**15**, R = H) by use of methyl 7-iodo-5-heptynoate (**14**) as the alkylating agent. Unfortunately, in this case we were unable to find conditions which gave clean monoalkylation. However, the monoalkylated products (**15** and **16**, R = CH_3) were sufficiently stable to be removed from the product mixture by evaporative distillation at 150° (0.005 mm). The volatile fraction of the product mixture was contaminated with the nonalkylated cyclopentanone, 3-(*trans*-3-hydroxy-1-octenyl)cyclopentan-1-one. This impurity was readily removed by hydrolysis of the methyl esters in compounds **15** and **16**, R = CH_3, followed by extraction of the neutral products. The free acids **15** and **16**, R = H, were then separated by chromatography on silica gel in 19.5% yield.



(±)-11,15-Deoxyprostaglandin E_2 (20, R = H).[11] An analogous sequence of reactions produced (±)-11,15-deoxy-PGE_2 (**20**, R = H). Hydroalumination[12] and bromination of the intermediate vinyl alane transformed 1-octyne into *trans*-1-bromo-1-octene (**17**, X = Br). Reaction



with lithium gave the corresponding lithium reagent (**17**, X = Li), which was converted to the cuprate **18** by treatment with cuprous iodide. This dialkylcopper lithium reagent was then treated with cyclopent-2-enone and the enolate ion trapped with trimethylsilyl chloride to yield the enol ether **19** in 97% yield. This silyl ether was then alkylated with methyl 7-bromo-*cis*-5-heptenoate (**9**) to yield (±)-11,15-deoxy-PGE_2 methyl ester (**20**, R = CH_3) in 60% yield. Saponification gave the free acid, (±)-11,15-deoxy-PGE_2 (**20**, R = H).

Acknowledgments. The authors wish to thank Dr. A. Van Horn and Mr. D. Wren for the preparation of additional samples of 3-(*S*)-*trans*-iodo-1-octen-3-ol and methyl *cis*-7-bromohept-5-enoate, and Dr. L. Tökés, Dr. M. Maddox, Mrs. J. Nelson, Mr. B. Amos, and Mr. V. Hayashida for physical data.

Registry No.—**8**, 51751-82-7; **9**, 51751-83-8; (±)-**10**, 35120-22-0; (−)-**10**, 37794-69-7; **11**, 38698-63-4; **11a**, 51819-56-8; **12**, 51751-84-9; **13**, 51794-45-7; **14**, 31776-12-2; **15** (R = H), 51751-85-0; **16** (R = H), 51751-86-1; **17**, 51751-87-2; **19**, 51751-88-3; **20** (R = CH_3), 51751-89-4; **20** (R = H), 40098-57-5; (*S*)-*trans*-1-iodo-1-octen-3-ol, 39647-93-3; 11-deoxy $PGF_{2\alpha}$ methyl ester, 33854-16-9; *ent*-11-deoxy-15-*epi*-$PGF_{2\alpha}$ methyl ester, 51751-90-7; (±)-*trans*-1-iodo-1-octen-3-ol, 39647-88-6.

Miniprint Material Available. Full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the miniprinted and supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036.

Experimental Section[13]

(13) Infrared spectra were recorded with a Perkin-Elmer 237B grating spectrometer. Nmr spectra were obtained with a Varian HA-100 instrument in deuteriochloroform with TMS as internal standard unless otherwise indicated. Mass spectra were recorded on Atlas werke CH-4 or CH-7 spectrometers. Combustion analyses were performed by the Syntex Analytical Laboratory.

(±)11-Desoxy Prostaglandin E_2 and (±)11-desoxy-15-epi Prostaglandin E_2 methyl esters (10 and 11). A solution of 5.0 mmol. of the achiral cuprate 2 was prepared as previously described.[4] This solution was cooled to -78° and treated with 0.396 g of cyclopent-2-enone in 3 ml of ether. The reaction was stirred at -78° for 15 min. and then diluted with 25 ml of THF. Trimethylchlorosilane (3 ml) and triethyl amine (4 ml) were added and the reaction mixture allowed to warm to 0°, and then poured into 300 ml of hexane and 200 ml of ice water. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was dissolved in 20 ml of DMSO and the silyl ether recovered by extraction with hexane (4 x 50 ml). The combined hexane extracts were washed twice with 100 ml of saturated sodium bicarbonate, dried over sodium sulfate and concentrated in vacuo to yield the silyl enol ether (8).

The crude silyl ether (8) was dissolved in 10 ml of THF and added to a mixture of lithium amide prepared from 82 mg of lithium, 80 ml of ammonia, 30 ml of THF and a trace of ferric nitrate. After 20 min at reflux, 4.0 g of methyl cis-7-bromo-5-heptanoate in 5 ml of THF was added over 30 sec. The reaction mixture was allowed to reflux for 3 min. and then quenched with ammonium chloride. A stream of nitrogen was used to remove the ammonia, and when the reaction mixture reached -15°, it was poured into a slurry of 200 g of ice, 150 ml of ether and 50 ml of acetic acid. The organic layer was separated and the aqueous layer extracted with 150 ml of ether. The combined ethereal solutions were treated with 20 ml of acetic acid, 20 ml of water and 50 ml of methanol, and then stirred at room temperature for 1 hr. The ether solution was then washed twice with 300 ml of brine, dried over sodium sulfate and concentrated in vacuo. Toluene (150 ml) was added and removed in vacuo to azeotrope the acetic acid. The resulting residue was chromatographed on 200 g of silica gel eluting with 20 to 30% ethyl acetate/hexane (v/v) · 0.370 g (21%) of (±)11-desoxy-15-epi-PGE_2 methyl ester (11) was eluted first: ir (film) 3500 (OH) and 1740 cm^{-1} (C=O and CO_2CH_3); nmr δ 5.6 (m, 2, trans CH=CH), 5.4 (m, 2, cis CH=CH), 4.1 (m, 1, C_{15}-H) 3.67 (s, 3, CO_2CH_3) and 0.90 ppm (t, 3, J=6Hz, CH_3); mass spectrum (70 eV) m/e (rel intensity) 350 (5), 332 (65), 300 (14), 279 (2), 191 (23), 109 (47) and 83 (100).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.16; H, 9.69.

0.429 g (26%) of (±)11-Desoxy PGE_2 methyl ester (10) was eluted next: ir (film) 3500 (OH) and 1740 cm^{-1} (C=O and CO_2CH_3); nmr δ 5.6 (m, 2, trans CH=CH), 5.4 (m, 2, cis CH=CH), 4.1 (m, 1, C_{15}-H), 3.67 (s, 3, CO_2CH_3) and 0.90 ppm (t, 3, J=6Hz, CH_3); mass spectrum (70 eV) m/e (rel intensity) 350 (1), 332 (10), 300 (5), 279 (5), 191 (2), 109 (87) and 83 (100).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.20; H, 9.86.

(-)11-Desoxy Prostaglandin E_2 and (+)11-desoxy-8,12-epi Prostaglandin E_2 methyl esters (10 and 11a). A solution of 2.64 g of (+)trans-1-iodo-1-octen-3-ol in 10 ml of isopropenyl methyl ether was cooled to 0° and treated with 3 drops of dichloroacetic acid. After 15 min, the ice bath was removed and the reaction allowed to continue at room temperature for 1 hr. Ten drops of triethyl amine were added and the excess isopropenyl methyl ether removed in vacuo.

The residue was dissolved in 20 ml of ether, cooled to -78° and treated with 14 ml of 1.6 N t-butyl lithium over a 10 min period under argon. After stirring at -78° for 20 min, this solution of vinyl lithium reagent was transferred via a double-tipped needle to a second flask containing a solution of 1.30 g of copper pentyne and 4 ml of HMP in 50 ml of ether. The second reaction vessel was also cooled in a dry ice/acetone bath and equipped with a mechanical stirrer. Following the transfer of the vinyl lithium reagent, the reaction was stirred at -78° for 20 min and then treated with 0.80 g of cyclopent-2-enone in 4 ml of ether. After another 15 min at -78°, 40 ml of THF, 4 ml of chlorotrimethyl silane and 3 ml of HMPA were added to the reaction mixture. The cooling bath was removed and the solution allowed to warm to 10° over 30 min. This mixture was then poured into 300 ml of hexane, 5 ml of triethyl amine and 300 ml of ice water. The organic phase was separated, dried over sodium sulfate and concentrated in vacuo. The oily residue thus obtained was dissolved in 10 ml of hexane, cooled to 0° and filtered to remove the precipitated copper pentyne. The filtrate was concentrated in vacuo to yield silyl enol ether 8 of sufficient purity for the alkylation reaction.

A solution of 82 mg of lithium in 110 ml of ammonia and 30 ml of THF was converted to lithium amide by addition of a crystal of ferric nitrate. Upon disappearance of the blue color, the silyl enol ether (8) from above in 10 ml of THF was added. This reaction mixture was stirred at -30° for 10 min and then treated with 4.0 g of methyl cis-7-bromohept-5-enoate in 5 ml of THF. This addition required 15 sec and the reaction was allowed to stir at -30° for an additional 2 min. The reaction was quenched by addition of ammonium chloride and the ammonia evaporated under a stream of nitrogen. The residue was poured into 300 ml of ether, 200 ml of ice and 80 ml of acetic acid. The organic layer was separated and the aqueous layer extracted twice with 100 ml ether. The combined ether extracts were treated with 50 ml of acetic acid and 30 ml of water and stirred at room temperature for one hour. The ethereal solution was washed with brine, dried over sodium sulfate and concentrated in vacuo. Toluene (200 ml) was then evaporated in vacuo from the residue to azeotrope any acetic acid present. The resulting residue was chromatographed on 300 g of silica gel, employing a continuous gradient of 15 to 25% ethyl acetate-hexane to yield 11-desoxy prostaglandin E_2 and 11-desoxy-8,12-epi-prostaglandin E_2 methyl esters (10 and 11). 0.446 g (13%) of (-)11-desoxy-8,12-epi-prostaglandin E_2 methyl ester (11a) was eluted first: $[\alpha]^{25}_D$ +43.6° (C 0.65, CH_3OH); ir (film) 3500 (OH) and 1740 cm^{-1} (C=O and CO_2CH_3); nmr δ 5.6 (m, 2, trans CH=CH), 5.4 (m, 2, cis CH=CH), 4.1 (m, 1, C_{15}-H) 3.67 (s, 3, CO_2CH_3) and 0.90 ppm (t, 3, J = 6Hz, CH_3); mass spectrum (70 eV) m/e (rel intensity) 350 (1), 332 (5), 300 (3), 279 (2), 191 (16), 109 (50) and 83 (100).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.68; H, 9.78.

0.598 g (17%) of (-)11-Desoxy prostaglandin E_2 methyl ester (10) was eluted next: $[\alpha]^{25}_D$ -41.0° (C 0.43, CH_3OH); ir (film) 3500 (OH) and 1740 cm^{-1} (C=O and CO_2CH_3); nmr δ 5.6 (m, 2, trans CH=CH), 5.4 (m, 2, cis CH=CH), 4.1 (m, 1, C_{15}-H), 3.67 (s, 3, CO_2CH_3) and 0.90 ppm (t, 3, J = 6Hz, CH_3); mass spectrum (70 eV) m/e (rel intensity) 350 (1), 332 (5), 300 (3), 278 (2), 191 (16), 109 (50) and 83 (100).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.19; H, 9.98.

Methyl-(+)9α-hydroxy-15-ketoprosta-5(c),13(t)-dienoate (12). A solution of 0.160 g of 11-desoxy PGE_2 methyl ester (10) in 6 ml of THF was cooled to -35° and treated with 2.0 ml of 0.5 N potassium tri-sec-butyl borohydride in THF with magnetic stirring. After 40 min at -30°, the reaction was quenched by addition of 2 ml of acetone. The reaction mixture was diluted with 100 ml of ice water and extracted three times with 75 ml ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated at reduced pressure. The residue was dried at 50°/0.01 mm to remove tri-sec-butyl borane and then chromatographed on 70 g of silica gel. Elution with 10 to 20% (v/v) ethyl acetate/hexane gave 0.094 g (59%) of 11-desoxy $PGF_{2\alpha}$ methyl ester: $[\alpha]^{25}_D$+69.6° (C 0.287, CH_3OH); ir (film) 3450 (OH) and 1735 cm^{-1} (CO_2CR_3); nmr δ 5.45 (m, 4, vinyl), 4.20 (m, 1, C_{15}-H), 4.05 (m, 1, C_9-H), 3.65 (s, 3, CO_2CH_3) and 0.87 ppm (t, 3, J = 6Hz, CH_2CH_3); mass spectrum (70 eV) m/e (rel intensity) 352 (1), 334 (4), 316 (20), 281 (5), 175 (40) and 67 (100).

Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.22; H, 10.37.

A solution of 0.070 g of 11-desoxy $PGF_{2\alpha}$ methyl ester and 0.160 g of DDQ in 5 ml of dioxane was heated at 55° under nitrogen for 4 hrs. The reaction mixture was cooled to room temperature, diluted with 100 ml of 5% aqueous sodium bisulfite and extracted twice with 100 ml of ether. The ether extracts were dried over sodium sulfate and concentrated in vacuo. The resulting residue was chromatographed on 70 g of silica gel and elution with 10 to 25% ethyl acetate/hexane gave 0.060 g (86%) of methyl 9α-hydroxy-15-ketoprosta-5(c),13(t)-dienoate (12): $[\alpha]^{25}_D$+89.1° (C 0.547, CH_3OH); uv (CH_3OH) 230 mμ (ε 12,600); ir (film) 3470 (OH), 1740 (CO_2CH_3), 1679 and 1625 cm^{-1} (CH=CH-C=O); nmr δ 6.68 (dd, 1, J = 16 and 8Hz, CH=CHCO); 6.07 (d, 1, J = 16Hz, CH=CHC=O), 5.38 (m, 2, cis CH=CH), 4.23 (m, 1, C_9-H), 3.65 (s, 3, CO_2CH_3) and 0.88 ppm (t, 3, J = 6Hz, CH_2CH_3); mass spectrum (70 eV) m/e (rel intensity) 350 (4), 332 (5), 226 (35), 191 (40) and 99 (100).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.72; H, 9.82.

Methyl(-)ent-9α-hydroxy-15-ketoprosta-5(c),13(t)-dienoate (13). In a similar reaction to that described above, 0.170 g of 11-desoxy-8,12-epi-PGE_2 methyl ester (11) was reduced with potassium tri-sec-butyl borohydride to 0.133 g (78%) of ent-11-desoxy-15-epi $PGF_{2\alpha}$ methyl ester: $[\alpha]^{25}_D$ -51.4° (C 0.535, CH_3OH); ir (film) 3450 (OH) and 1735 cm^{-1} (CO_2CH_3); nmr δ 5.45 (m, 4, vinyl), 4.20 (m, 1, C_{15}-H), 4.05 (m, 1, C_9-H), 3.64 (s, 3, CO_2CH_3) and 0.87 ppm (t, 3, J = 6Hz, CH_2CH_3); mass spectrum (70 eV) 334 (4), 316 (22), 26 (5), 119 (79) and 67 (100).

Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.25; H, 10.18.

In the manner described above for the preparation of methyl 9α-hydroxy-15-ketoprosta-5(c),13(t)-dienoate (12), 0.104 g of ent-11-desoxy-15-epi-$PGF_{2\alpha}$ methyl ester was oxidized with DDQ in dioxane to yield after silica gel chromatography 0.065 g (60%) of methyl ent-9α-hydroxy-15-ketoprosta-5(c),13(t)-dienoate (13): $[\alpha]^{25}_D$ -94.0° (C 0.59, CH_3OH); uv (CH_3OH) 231 mμ (ε 14,100); ir (film) 3470 (OH), 1740 (CO_2CH_3), 1670 and 1625 cm^{-1} (CH=CH-C=O); nmr δ 6.68 (dd, 1, J = 16 and 8Hz, CH=CHC=O); 6.07 (d, 1, J = 16Hz, CH=CHC=O), 5.38 (m, 2, cis CH=CH), 4.23 (m, 1, C_9-H), 3.65 (s, 3, CO_2CH_3) and 0.88 ppm (t, 3, J = 6Hz, CH_2CH_3); mass spectrum (70 eV) m/e (re intensity) 350 (4), 332 (5), 226 (35), 191 (40) and 99 (100).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.64; H, 9.70.

(±)5,6-Dehydro-11-desoxyprostaglandin E_2 (15, R = H). As described above, 2.64 g of (±)-trans-1-iodo-1-octen-3-ol was converted via the lithio derivative to the mixed cuprate reagent 2 and then to the (±) silyl enol ether 8. This intermediate (8) was subjected immediately to the following alkylation procedure.

A suspension of lithium amide prepared from 0.10 g of lithium, 125 ml of liquid ammonia, 30 ml of tetrahydrofuran and a trace of ferric nitrate was cooled to -40° and treated with crude silyl ether 8 in 10 ml of tetrahydrofuran. After 10 min at -40°, a solution of 9.0 g of methyl 7-iodo-5-heptynoate (14) in 10 ml of tetrahydrofuran was added to the reaction mixture. The reaction was allowed to proceed at -40° for 5 min, at -30° for 5 min and then quenched with ammonium chloride. The ammonia was evaporated under a stream of nitrogen until the pot temperature reached -15°. The residue was poured into 300 ml of ice water and 80 ml of acetic acid. This mixture was stirred for 1 hr and then extracted with ether (2 x 100 ml). The combined ether layers were washed with brine, dried over sodium sulfate and concentrated in vacuo. 100 ml of toluene was added and then removed in vacuo to azeotrope any acetic acid present. The resulting residue (3.1 g) was subjected to evaporative distillation (150°/0.005 mm) to yield 0.942 g of volatile products. This mixture of monoalkylated products (15 and 16, R = CH_3) could not be chromatographically separated, hence was hydrolysed to the carboxylic acid.

A solution of 0.942 g of distilled esters 15 and 16, R = CH_3, 10 ml of water, 10 ml of methanol and 0.70 g of potassium hdyroxide was stirred at room temperature for 3 hrs. The organic solvents were removed in vacuo and the reaction mixture diluted with 50 ml of water. The aqueous solution was extracted with ether (2 x 100 ml), acidified to pH4 and extracted with ethyl acetate (3 x 100 ml). The combined ethyl acetate extracts were washed with brine, dried over sodium sulfate and concentrated in vacuo. The resulting oil was chromatographed on 200 g of silica gel, eluting with a gradient of 5/2/93 to 25/4/71% ethyl acetate/acetic acid/hexane (V/V) mixtures, and gave acids 15 and 16. 0.312 g (9.3%) of (±)5,6-Dehydro-11-desoxy-15-epiprostaglandin E_2 (16, R = H) was eluted first: ir (film) 1740 (C=O) and 1710 cm^{-1} (CO_2H); nmr δ 5.65 (m, 2, CH=CH), 4.1 (m, 1, C_{15}-H) and 0.88 ppm (s, 3, J = 6Hz, CH_3); mass spectrum (70 eV) m/e (rel intensity) 334 (2), 316 (10), 263 (37), 244 (49), 181 (50), 163 (83) and 43 (100).

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Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.48; H, 8.96.

0.342 g (10.2%) of (±)5,6-Dehydro-11-desoxyprostaglandin E_2 (15, R = H) was eluted next: ir (film) 1740 (C=O) and 1710 cm^{-1} (CO_2H); nmr δ 5.65 (m, 2, CH=CH), 4.1 (m, 1, C_{15}-H) and 0.88 ppm (t, 3, J = 6Hz, CH_3); mass spectrum (70 eV) m/e (rel intensity) 334 (2), 316 (10), 263 (42), 244 (51), 181 (67), 163 (100), 43 (90).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.63; H, 8.88.

(±)3-(trans-1-octenyl)-1-trimethyl siloxy cyclopentene (12). 7.64 g of trans-1-bromo-1-octene (40 mmol) in 12 ml of ether was added over 30 min to 0.79 g of lithium wire containing 1% sodium in 40 ml of ether under argon with magnetic stirring. The reaction temperature was held at -5 to -10° for 2 hr. This solution was then added to a slurry of 3.80 g (20 mmol) of cuprous iodide in 20 ml of THF at -35°. After stirring at -35° for 15 min, a solution of 1.64 g (20 mmol) of cyclopent-2-enone in 4 ml of THF was added to the reaction mixture. Following a 20 min period at -40°, 5 ml of chlorotrimethyl silane was added to the reaction mixture and the cooling bath removed. On warming to room temperature, the reaction mixture was poured into 200 ml of hexane, 3 ml of triethyl amine and ice water. The hexane solution was separated, washed with saturated bicarbonate, dried over sodium sulfate and concentrated in vacuo. Short path distillation gave 5.211 g (97%) of enol ether (19): bp 93-98° (0.1 mm); ir (film) 1640 cm^{-1} (OC=CH); nmr (CCl_4) 5.30 (m, 2, CH=CH), 4.42 (m, 2, OC=CH), 3.2 (m, 1, C=CH-CH-CH=CH), 0.91 (t, 3, CH_2CH_3), and 0.20 ppm [s, 9, Si(CH_3)]; mass spectrum (70 eV) m/e (rel intensity) 266 (8), 193 (25), 181 (100), 75 (18), 73 (90).

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Anal. Calcd for $C_{16}H_{30}OSi$: C, 72.10; H, 11.35. Found: C, 71.97; H, 11.45.

(±)11,15-Desoxyprostaglandin E_2 methyl ester (20, R = CH_3). A solution of 1.33 g of silyl enol ether 19 (5 mmol) in 10 ml of tetrahydrofuran was added to a suspension of lithium amide prepared from 73 mg of lithium, 80 ml of ammonia, 30 ml of tetrahydrofuran and a trace of ferric nitrate. The reaction mixture was stirred magnetically and protected from atmospheric moisture by means of a nitrogen atmosphere. After stirring for 10 min at -35°, a solution of 4.45 g (20 mmol) of methyl cis-7-bromo-5-heptenoate in 5 ml of tetrahydrofuran was added over a 30 sec interval. Following an additional reaction period of 3 min at -35°, the reaction was quenched with ammonium chloride. The ammonia was evaporated under a stream of nitrogen and the resulting residue poured into 200 ml of ice water and 40 ml of acetic acid. This solution was then extracted with three 200 ml portions of ether, the combined ethereal extracts washed with brine, dried over sodium sulfate and concentrated in vacuo. Toluene (100 ml) was added and the mixture evaporated again to remove acetic acid. This residue was chromatographed on 300 g of silica gel, eluting with a gradient of 5-20% ethyl acetate-hexane (v/v) to yield 0.986 g (60%) of prostaglandin 20, R = CH_3. A small

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sample of 20, R = CH_3 was evaporatively distilled for spectral analysis: ir (CCl_4) 1750 cm^{-1} (CO_2CH_3 and C=O); nmr δ 5.4 (m, 4, CH=CH), 3.65 (s, 3, OCH_3), and 0.89 ppm (t, 3, CH_3); mass spectrum (70 eV) m/e (rel intensity) 334 (2), 303 (3), 194 (20) and 109 (100).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.14; H, 10.25.

11,15-Desoxy Prostaglandin E_2 (20, R = H). A solution of 0.227 g of potassium hydroxide, 10 ml of water, 10 ml of tetrahydrofuran, 3 ml of methanol and 0.304 g of keto ester 20, R = CH_3 was stirred under nitrogen for 4 hr. Tlc analysis showed the absence of starting ester and the reaction mixture was diluted with 100 ml of water, extracted twice with 200 ml of ether, acidified to pH2 with concentrated hydrochloric acid, and extracted three times with 100 ml of ethyl acetate. The combined ethyl acetate solution were washed with brine, dried over sodium sulfate and concentrated in vacuo. The residue was evaporatively distilled at 150°/9.005 mm to yield 0.248 g of 20, R = H: ir (CCl_4) 1750 (C=O) and 1715 cm^{-1} (CO_2H); nmr δ 8.5 (s, 1, CO_2H), 5.4 (m, 4, CH=CH) and 0.89 ppm (t, 3, CH_3); mass spectrum m/e (rel intensity) 320 (1), 302 (1), 194 (7) and 109 (100).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 75.74; H, 10.12.

Remit check or money order for $4.00 for photocopy of $2.00 for microfiche, referring to code number JOC-74-2506.

References and Notes

(1) (a) Contribution No. 434 from the Institute of Organic Chemistry, Syntex Research. (b) Studies in Prostaglandins, No. 38. (c) The contents of this paper were the subject of lectures by J. Fried, presented at the University of Southern California (Nov 17, 1972), the University of California, Santa Cruz (Jan 8, 1973), and the Eidgenössische Technische Hochschule (Zurich) (May 9, 1973).

(2) For reviews of conjugate addition of organocuprates, see G. Posner, *Org. React.*, **19**, 1 (1972), and V. F. Nort, *Synthesis*, 63 (1972).

(3) For enolate trapping and alkylation see G. Stork, *Pure Appl. Chem.*, **17**, 393 (1968), and G. Stork, P. Rosen, N. Goodman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965).

(4) A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Amer. Chem. Soc.*, **94**, 7827, 9256 (1972).

(5) C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzotti, and M. Casey, *J. Amer. Chem. Soc.*, **94**, 3643 (1972).

(6) Likewise the use of 4-(*R*)-hydroxycyclopent-2-enone should give PGE_2 as the predominant prostaglandin product.

(7) For other syntheses of 11-deoxyprostaglandin E_2 see (a) E. J. Corey and T. Ravindranathan, *Tetrahedron Lett.*, 4753 (1971); (b) P. Crabbé and A. Guzman, *ibid.*, 115 (1972); (c) J. Bagli and T. Bogri, *ibid.*, 3815 (1972); (d) N. A. Abraham, *ibid.*, 451 (1973); (e) P. A. Grieco and J. J. Reap, *J. Org. Chem.*, **38**, 3413 (1973); (f) F. H. Lincoln, W. P. Schneider, and J. E. Pike, *ibid.*, **38**, 951 (1973).

(8) R. M. Coates and R. L. Sowerly, *J. Amer. Chem. Soc.*, **93**, 1027 (1971), reported the very rapid, regiospecific alkylation of cyclopentanone enolates under similar conditions.

(9) E. J. Corey and D. J. Beames, *J. Amer. Chem. Soc.*, **94**, 7210 (1972).

(10) This reduction was performed by A. Prince in these laboratories.

(11) For another synthesis of 11,15-deoxyprostaglandin E_2 see K. F. Bernady and M. J. Weiss, *Tetrahedron Lett.*, 4083 (1972), and P. A. Grieco and J. J. Reap, *J. Org. Chem.*, **38**, 3413 (1973).

(12) G. Zweifel and C. G. Whitney, *J. Amer. Chem. Soc.*, **89**, 2753 (1967).

Pyrolysis of Spirotrithianes

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Pyrolysis of spirotrithianes **3–7** at reduced pressure gave volatile mixtures consisting almost entirely of cyclic thioketones and their enethiols. At higher temperatures volatile products were mixtures of mercaptans and olefins. The nonvolatile residue of higher temperature pyrolysis of cyclohexanethione trimer contained dibenzothiophene, tetrahydrodibenzothiophene, octahydrodibenzothiophene,and spiro-2,2-pentamethylenebenzodithiolane (**13**). Bicyclo[2.2.1]heptane-2-thione (**1**) is a further example of a relatively stable thioketone.

Several methods for preparing aliphatic thioketones have been reported recently.[1-5] Each suffers from lack of generality. The absence of a general synthetic method for preparing thioketones, their instability, and the disagreeable odor of their intermediates all have slowed the investigation of the chemistry of the thiocarbonyl group. In the course of synthesis of thiols we prepared norbornanethione (**1**) by pyrolysis of trithiane **3** in good yield despite previous reports[6,7] that pyrolysis of trithianes is unsatisfactory for preparation of aliphatic thioketones. The results of pyrolyzing the structurally related spirotrithianes **4–7** at reduced pressure are shown in Table I.

These pyrolyses were stopped after generating workable quantities of red distillate and were not necessarily pushed to completion. Thioketone content of products was estimated from the absorption maximum at about 500 nm and enethiol content was estimated from nmr spectra.

Table I
Pyrolyses at Reduced Pressure

Pyrolysis of	Pressure, mm	Pot temp, °C (external)	Time, min	% distilling	Composition of distillate: % thione	Composition of distillate: % enethiol
3	~20	210–293	60	85	91	
3′	10	240–278	198	43	96	<1
4	13	195–247	30	10	>13	34
5	13–17	290–310	10	68	*a*	
6	13	165–210	80	45	>34	12
7	10	180–260	95	23	~33	32

[a] Red liquid distillate rapidly crystallized to give trimer.