in 270 mL of THF containing 4.1 g of 10% Pd/C in suspension. After 24 h the suspension of product and catalyst was filtered on sintered glass under N_2 pressure and washed with 150 mL of THF and twice with 150 mL of acetonitrile. The grayish mixture was thoroughly dried on the filter in the N_2 stream and then kept under vacuum overnight. The precipitate was treated on the filter with two 100-mL portions of water. The resulting filtrate was stirred briefly with 600 mL of acetonitrile, forming two phases. The upper phase was separated and mixed with 1 L of acetonitrile. After 30 min the agaritine was collected on sintered glass, washed with 200 mL of acetonitrile and 200 mL of ether, and vacuum dried at room temperature for 24 h. An additional 10% of agaritine was obtained by again treating the catalyst on the filter with 300 mL of water, evaporating the filtrate under reduced pressure at room temperature to 50 mL, and precipitating agaritine by addition of 450 mL of acetonitrile. The second crop was filtered, washed, dried, and combined with the main portion. Agaritine was obtained as fine white needles containing 1 mol of water of crystallization:[12] yield 12.6 g (88%); mp 203–206 °C dec; $[\alpha]_D^{23}$ + 8° (c 9.89 in water) [corrected for water of crystallization: $[\alpha]_D^{23}$ + 9° (lit.[4] $[\alpha_D^{23}]$ +7°)].

Chromatographic properties and ^1H NMR spectra were identical with those of agaritine isolated from mushrooms[13] and agaritine obtained through the courtesy of the Upjohn Co.

Anal. Calcd for $C_{12}H_{17}N_3O_4 \cdot H_2O$: C, 50.52; H, 6.71; N, 14.73. Found: C, 50.54; H, 6.73; N, 14.98.

Registry No. **1a**, 619-67-0; **2**, 3705-42-8; **3**, 71426-47-6; **4a**, 2757-90-6; **4b**, 13523-77-8; **5a**, 71426-48-7; **5b**, 71426-49-8; **6**, 1155-62-0.

(12) The water of crystallization could not be removed by the usual drying methods without decomposition. An anhydrous product was obtained from the hydrated material by precipitating it from saturated aqueous solution with 4 volumes of 1-butanol–ethanol (1:3) and drying under vacuum at 40 °C: mp 206–209 °C dec (lit.[4] mp 205–208 °C). Anal. Calcd for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.70; H, 6.39; N, 15.61.

(13) Agaritine was isolated and purified by a modification of the method described in ref 4: P. Issenberg, unpublished work.

A Convergent Total Synthesis of (±)-Prostaglandin $F_{2\alpha}$ via Conjugate Addition and Regiospecific Enolate Trapping

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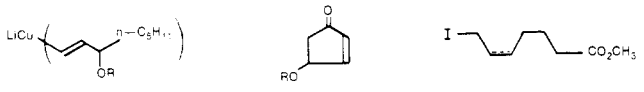
Received April 19, 1979

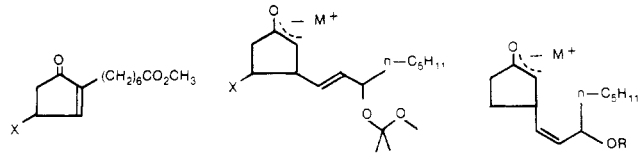
A convergent total synthesis of (±)-$PGF_{2\alpha}$ via the conjugate addition of the dioctenylcuprate reagent **7a**, derived from 1-iodo-3-hydroxyoct-1-*cis*-ene, to 4-[(*tert*-butyldimethylsilyl)oxy]cyclopent-2-en-1-one (**2a**) followed by regiospecific enolate trapping with ketene bis(methylthio)acetal monoxide (**18**) and stereospecific sulfenate–sulfoxide transformation is reported. The thioacetal intermediate **22**, after stereospecific reduction and hydrolysis, is converted to the known ketol **24** and then to (±)-$PGF_{2\alpha}$.

One of the simplest converging syntheses of prostaglandins is the regiospecific alkylation of the enolate initially generated by the conjugate addition of a selected vinyl cuprate (e.g., **1**, β chain) to a protected 4-hydroxycyclopent-2-enone (**2**) with an appropriate allyl or saturated halide (e.g., **3**, α chain). This attractive route has been investigated in our laboratories[1a,b] and by others[2a,b] for several years without success.[2c] The obstacles to overcome are alkylating the initially formed nonequilibrated enolate in any kind of resonable yield and retaining the 4-oxygen substituent under conditions where alkylation does occur.



1 **2a** R = $SiMe_2Bu$ **3**

Our attempts to realize this enolate trapping route were directed first to obtaining the requisite lithium dialkenylcuprate (**1**, R = CMe_2OMe) for conjugate addition to a 2-[(carbomethoxy)hexyl]-4-protected hydroxycyclopent-2-enone (**4a**). This was achieved by us[3] and others.[4]



4a X = $OCMe_2OMe$ **5a** X = H **6a** R = CMe_2OMe
b X = H **b** X = $OSiMe_2Bu$ **b** R = $SiMe_2Bu$

We found next that a lithium *cis*-dialkenylcuprate gave higher yields of conjugate addition which led to 13-*cis*-PGs with a high degree of stereoselectivity at C-15[5] as an added important benefit. Knowing that the cuprate-generated enolate (e.g., **6**) was present in the reaction mixtures in large amounts (≥70%) prior to protic quench, we attempted alkylations with allyl bromide and iodide under a variety of conditions but obtained no alkylation. The same results (no alkylation) were obtained when the cyclopentenone **2a** was used.[1b] We knew that the enolate, **5a**, could be trapped efficiently as the (trimethylsilyl)enol ether, and the regenerated enolate could then be alkylated.[1a] Later, reports[6] of α-alkylations of cuprate-

(1) (a) J. W. Patterson, Jr., and J. H. Fried, *J. Org. Chem.*, **39**, 2506 (1974); (b) A. F. Kluge, Syntex Postdoctoral Fellow, 1971–1972; J. G. Miller, Syntex Postdoctoral Fellow, 1972–1973; P. Konstantin, Syntex Postdoctoral Fellow, 1975–1976, unpublished results.

(2) (a) G. Stork and M. Isobe, *J. Am. Chem. Soc.*, **97**, 4745 (1975), ref 10; G. Stork and M. Isobe, *J. Am. Chem. Soc.*, *97*, 6260 (1975), ref 3 and private communication; (b) G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz, and D. J. Brunelle, *J. Am. Chem. Soc.*, **97**, 107 (1975), and references cited therein; (c) For complete reviews of prostaglandin synthesis through 1976, see A. Mitra, "The Synthesis of Prostaglandins", Wiley, New York, 1977, and J. S. Bindra and R. Bindra, "Prostaglandin Synthesis", Academic Press, New York, 1977.

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

(4) C. J. Sih, P. Price, R. Sood, R. G. Solomon, G. Peruzzotti, and M. Casey, *J. Am. Chem. Soc.*, **94**, 3643 (1972).

(5) A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 9256 (1972), and note added in proof; J. G. Miller, W. Kurz, K. G. Untch, and G. Stork, *J. Am. Chem. Soc.*, **96**, 6774 (1974).

(6) (a) P. A. Grieco and R. Finkelhor, *J. Org. Chem.*, **38**, 2100 (1973); (b) G. H. Posner and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 3076 (1973); (c) R. K. Boeckman, Jr., *J. Org. Chem.*, **38**, 4450 (1973).

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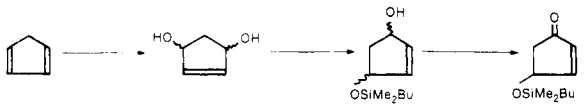
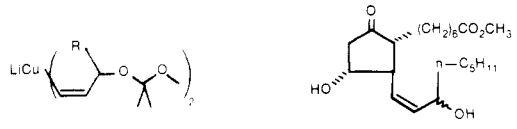
Scheme I



11 2a

generated enolates of other systems, particularly that of Boeckman wherein HMPA is added prior to addition of the alkylating reagent, prompted us to investigate the direct alkylation of the cuprate-generated enolate, using HMPA addition.[6c]

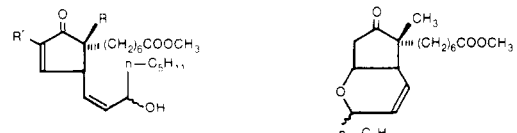
Conjugate addition of cuprate **7a** (3 equiv) to enone **4a**



7a R = n-C5H11
b R = n-C7H15

8a 15α-OH
b 15β-OH

followed by the addition of ca. 20% (vol) HMPA and methyl iodide (6 equiv) gave ca. 23% of the unmethylated products, **8a** and **8b**, and five mono- and dimethylated products (ca. 47%), **9a**, **9b**, **9c**, **10a**, and **10b**. All of these

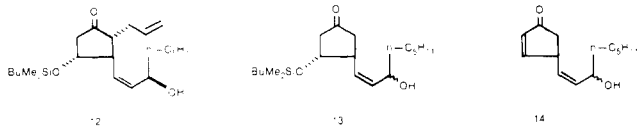


9a R = CH3, R' = H
b R = H, R' = CH3
c R = R' = CH3

10a 15α
b 15β

methylated products can be explained by initial loss of the 11-protected hydroxyl and subsequent methylation of the three possible enolates. The cyclic ethers resulted from Michael addition of the 15-hydroxyl group during workup.

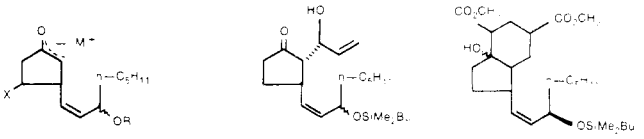
Cyclopentenone **2a** was prepared in four steps (Scheme I) from cyclopentadiene to 3,5-cyclopentendiols[7] to monosilyloxyenol **11** which was oxidized with manganese dioxide.[8b] Conjugate addition of cuprate **7** (2 equiv) to enone **2a** followed by the addition of 15% (vol) HMPA and allyl iodide (1.1 equiv) led to none of the 2-alkylated product **12**. Only the addition product **13** and the corresponding α,β-unsaturated enone **14** were formed.[8a]



12 13 14

Based on our studies, an enolate first formed via conjugate cuprate addition (e.g., **5a** or **6b**) is complex in nature and may involve copper in some way since no alkylation occurs with either methyl iodide or allyl iodide. The addition of HMPA to the reaction medium causes a change and provides a different enolate. However, this enolate (e.g., **15b**) undergoes proton transfer and β elimination at a rate faster than regiospecific alkylation and thus renders this route to the synthesis of prostaglandins (those with an 11-hydroxyl group) inoperative. Even the (*tert*-butyldimethylsilyl)oxy group was eliminated. House and Wilkins[9] have provided convincing evidence recently that the intermediate formed by the addition of Me_2CuLi to 3-methylcyclohex-2-enone is a lithium enolate. From our investigations, it seems that the nature of the intermediate formed by cuprate addition depends upon the structure of the alkenyl group (in these cases it carried an alkoxy or silyloxy substituent), the enone (cyclopentenone[10]), and, perhaps, the solubilizing ligand used [$P(OMe)_3$].

Although less desirable than regiospecifically alkylating the cuprate-generated enolate (e.g., **15b**) with a prostaglandin upper-chain synthon directly, an efficient total synthesis would still be realized if the enolate could be trapped with an electrophile that would provide an intermediate readily convertible to the PG, e.g., an acetaldehyde derivative. During previous studies, we found that the cuprate-generated enolate **15a** readily reacts with



15a X = H, R = SiMe2Bu
b X = OSiMe2Bu, R = SiMe2Bu

16

acrolein: not in a Michael condensation, but rather with the aldehyde to provide an allylic alcohol derivative **16**. That formaldehyde is an excellent trap for the cuprate-formed enolate was shown and utilized in a total synthesis of PGE_1 by Stork.[2a] Our intent had been that the acrolein would trap as a Michael acceptor, so, instead, we used methyl acrylate for this purpose. It was found that an ca. 47% yield of a mixture of bisadducts resulted; i.e., the anion α to the resulting ester condensed with another methyl acrylate which then cyclized to give **17**. Although very little of the expected primary product was obtained from these experiments, it was shown that a cyclopentanone cuprate generated enolate would regiospecifically react with a Michael acceptor without changing the reaction medium.[11]

We were encouraged by this result but had yet to determine whether this regiospecific Michael reaction would be successful with a 4-hydroxy-protected enolate. Two other investigations of Michael reactions with regiospecifically generated enolates have been reported, that of Boeckman[12] and Stork[13] wherein cyclohexanone enolates were trapped with α-trialkylsilyl vinyl ketones, and the sequence has been applied to syntheses of steroids. Thus, an intermediate enolate, **15b**, should be efficiently trapped with Me_3SiCl,[1a,2b,14] Ac_2O,[15] $ClPO(OEt)_2$,[2a,16] acyl chlorides,[17] aldehydes[18] (formaldehyde[2a]), and reactive Michael

(7) M. Korach, D. R. Nielson, and W. H. Rideout, "Organic Synthesis", Collect. Vol. V, Wiley, New York, 1973, p 414.

(8) (a) The synthesis of enone **2a** and these further enolate alkylation attempts were carried out by P. Konstantin, Syntex Postdoctoral Fellow, 1975–1976, unpublished results. (b) Another independent synthesis of enone **2a** has appeared: T. Tanaka, S. Kurozumi, T. Toru, S. Miura, M. Kobayashi, and S. Ishimoto, *Tetrahedron*, **32**, 1713 (1976).

(9) H. O. House and J. M. Wilkins, *J. Org. Chem.*, **41**, 4031 (1976).

(10) Patterson and Fried[1a] obtained a 47% yield of 11-deoxyprostaglandins by alkylation with 7-bromo-*cis*-heptenoate of an enolate generated from the corresponding silyl enol ether and a 60% yield of the analogous product lacking the C-15 hydroxyl group. Posner[2b] obtained a 10–20% yield of a similar 2,3-dialkylated cyclopentanone by alkylation with 7-iodo-*cis*-heptenoate of the divinylcuprate-generated enolate. Some difference between the enolates is evidenced depending upon the mode of generation, i.e., cuprate generated or otherwise. Cuprate-generated enolates from cyclohexenones exhibit smaller differences, e.g., ref 2b and 6c.

(11) These enolate trapping experiments with acrolein and methyl acrylate were carried out by J. G. Miller, Syntex Postdoctoral Fellow, 1972–1973.

(12) R. K. Boeckman, Jr., *J. Am. Chem. Soc.*, **95**, 6867 (1973); **96**, 6179 (1974).

(13) G. Stork and J. Singh, *J. Am. Chem. Soc.*, **96**, 6181 (1974).

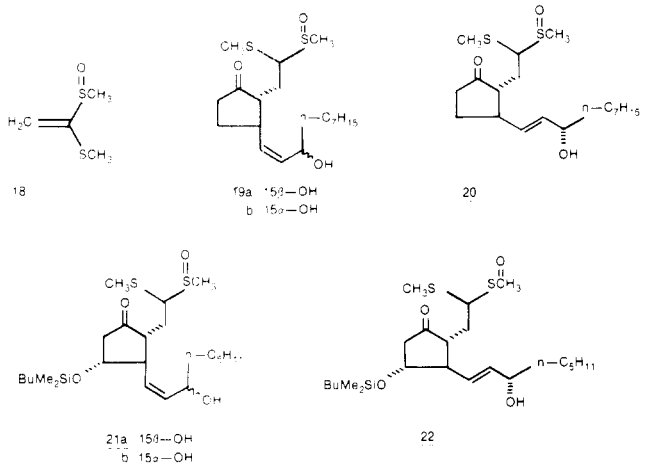
(14) E. S. Binkley and C. H. Heathcock, *J. Org. Chem.*, **40**, 2156 (1975).

(15) (a) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966); (b) H. Riviere and P. W. Tang, *Bull. Soc. Chim. Fr.*, 2455 (1973); (c) D. J. Goldsmith and I. Sakano, *Tetrahedron Lett.*, 2857 (1974).

(16) (a) R. E. Ireland and G. Pfister, *Tetrahedron Lett.*, 2145 (1969); (b) D. C. Muchmore, *Org. Synth.*, **52**, 109 (1972).

acceptors.[12,13] The regeneration of the enolate from any of the enol derivatives cannot be used for PG synthesis since the enolate itself is sufficiently basic to cause rapid proton transfer and immediate β elimination of the 4-hydroxy-protected substituent.[19] However, the aldol from the formaldehyde trap and, presumably, a suitable Michael adduct, both of which produce the C-7,8 carbon–carbon bond regiospecifically, can be utilized to synthesize an 11-hydroxylated PG.

We report here on one of these converging regiospecific enolate trapping syntheses, utilizing an excellent Michael acceptor, ketene bis(methylthio)acetal monoxide (**18**),

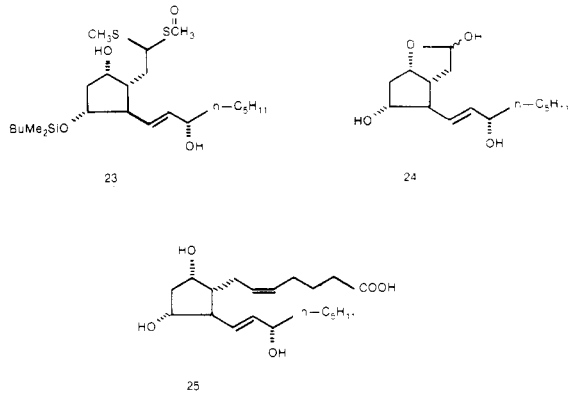


which was introduced by Schlessinger[20] for the synthesis of 1,4-dicarbonyl compounds in which one of the carbonyl groups is an aldehyde. The approach consists of (a) employing the easily adaptable highly stereoselective *cis*-dialkenylcuprate conjugate addition,[5,21] (b) regiospecific trapping of the kinetic enolate with ketene bis(methylthio)acetal monoxide (**18**) which provides a masked aldehyde suitable for conversion to the PG α chain with the known Wittig condensation, and (c) carrying out the stereospecific sulfenate–sulfoxide rearrangement[22] to complete a total synthesis of $PGF_{2\alpha}$.

Cyclopentenone was added to the cuprate **7b**, derived from the methoxyisopropyl ether[1b,5] of 1-iododec-1-*cis*-en-3-ol,[23] at −78 °C and, after 10 min, the ketene acetal **18** was added. After workup, the products **19a** and **19b** were isolated by preparative high pressure LC in 43 and 8% yields, respectively (84:16). Similarly, the cuprate **7a**, derived from the methoxyisopropyl ether of 1-iodooct-1-*cis*-en-3-ol,[5] was reacted sequentially with cyclopentenone **2a** and the ketene acetal **18**. After workup, the products **21a** and **21b** were isolated by preparative high pressure LC in 45 and 8% yields, respectively (85:15). Thus, the cuprate-generated kinetic enolate was trapped and, more importantly, the 4-(*tert*-butyldimethylsilyl)oxy group was not eliminated. It is noted that isolation of pure **19a** and **21a** is facilitated by the distinct separation (TLC and high pressure LC) that occurs between the isomers of each pair, **19a** and **19b** and **21a** and **21b**.

Application of the sulfenate–sulfoxide rearrangement,[22] i.e., reaction of the 13-*cis*-allylic alcohols **19a** and **21a** with an arylsulfenyl chloride to provide the 13-α-sulfoxides followed by sulfenate cleavage without purification produced the 13-*trans*-allylic alcohols **20** and **22** in good yields (90 and 74%). The transformations of **21a** to **22** required a lower reaction temperature for the first step. It was necessary to be able to carry out these sulfenate–sulfoxide rearrangements with these intermediates containing the ketene thioacetal functionality at this stage in the synthetic sequence in order to avoid potential problems with other nonprotected hydroxyl groups, e.g., either or both at C-9 and C-11.

The remaining steps of this synthesis of (±)-$PGF_{2\alpha}$ were completed straightforwardly. Reduction of the ketone **22** with L-Selectride gave the 9α-hydroxy derivative **23** with



virtual stereospecificity (95% yield), which on treatment with 9 N HCl in THF gave the known lactol[24] **24a** by concomitant hydrolysis of the 11-silyloxy ether and the thioketal monoxide. Without purification, lactol **24a** was treated via established chemistry[24] with (4-carboxy-*n*-butyl)triphenylphosphorane[25] to give (±)-$PGF_{2\alpha}$ (58%), mp 55–57 °C (lit.[26] mp 55–56 °C), which exhibited TLC R_f's, in all systems examined,[27] identical with those of an authentic sample of (−)-$PGF_{2\alpha}$ (Ono Pharmaceutical Co., Osaka, Japan).

This relatively simple converging synthesis leads to (±)-$PGF_{2\alpha}$ from the key step of a conjugate addition–regiospecific enolate trap in an overall yield of 18% in six steps. This synthesis should provide natural (−)-$PGF_{2\alpha}$ stereoselectively by using enantiomer (3*R*)-cuprate, **7a**,[5] and it should produce (−)-$PGF_{2\alpha}$ stereospecifically[29] by using (4*R*)-enone **2a**.[8b,28]

Experimental Section

Infrared (IR) spectra were recorded on a Perkin-Elmer 137 or 237B grating spectrometer. Nuclear magnetic resonance (NMR)

(17) A 10% yield of a 2-(carbomethoxy)-3-octenyl-4-[(tetrahydropyranyl)oxy]cyclopentanone resulted from kinetic enolate trapping with methyl chloroformate, see T. Toru, S. Kurozumi, T. Tanaka, S. Miura, M. Kobayashi, and S. Ishimoto, *Tetrahedron Lett.*, 4087 (1976), and for an enolate trap with ω-(carboethoxy)hexanoyl chloride (no yield given), see T. Tanaka, S. Kurozumi, T. Toru, M. Kobayashi, S. Miura, and S. Ishimoto, *Tetrahedron Lett.*, 1535 (1975).

(18) (a) F. Näf, R. Decorzant, and W. Thommen, *Helv. Chim. Acta*, **58**, 1808 (1975); K. K. Heng and R. A. J. Smith, *Tetrahedron Lett.*, 589 (1975).

(19) J. W. Patterson, private communication.

(20) J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet, P. J. Wepple, and R. H. Schlessinger, *Tetrahedron Lett.*, 4711 (1973).

(21) W. Bornatsch and K. G. Untch, *Prostaglandins*, **14**, 617 (1977); (b) C. Lüthy, P. Konstantin, and K. G. Untch, *J. Am. Chem. Soc.*, **100**, 6211 (1978).

(22) J. G. Miller, W. Kurz, K. G. Untch, and G. Stork, *J. Am. Chem. Soc.*, **96**, 6774 (1974), and ref 21b.

(23) We thank W. Kurz, Syntex Research, for this compound.

(24) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).

(25) We thank A. F. Kluge, Syntex Research, for providing the phosphonium salt.

(26) J. Fried, C. H. Lin, J. C. Sih, P. Dalven, and G. F. Cooper, *J. Am. Chem. Soc.*, **94**, 4342 (1972).

(27) In addition to normal phase TLC [see M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **241**, 257 (1966)], comparisons using reverse-phase TLC were made (80% MeOH–H_2O, HCO_2H, trace, and 50% MeOH–0.1 N NaCl).

(28) (4*R*)-4-Hydroxycyclopent-2-enone has been synthesized from D-(−)-tartaric acid, K. Ogura, M. Yamashita, and G. Tsuchihashi, *Tetrahedron Lett.*, 759 (1976).

(29) See G. Stork and T. Takahashi, *J. Am. Chem. Soc.*, **99**, 1275 (1977), ref 9.

Table I. ^{13}C NMR δ ($CDCl_3$)[a]

carbon no.	19a	19b	20	21a	21b	22	23
6	62.42	67.98	62.78	62.42	67.46	62.61	64.53
7	24.80	25.42	25.62	24.87	25.19	25.33	25.23
8	51.62	54.71	51.23	51.20	51.98	51.18	43.14
9	218.27		218.40	213.46	215.31	214.93	72.11
10	37.16	36.54	37.26	46.91	45.25	37.39	37.48
11	28.58	32.35	28.45	72.92	79.26	77.03	75.68
12	42.98	44.44	47.37	50.91	55.10	47.11	48.28
13	134.43	131.73	132.51	132.41	133.55	131.92	131.76
14	135.47	134.78	135.34	138.72	135.04	136.62	134.91
15	69.28	68.27	71.91	68.07		72.75	72.20
16	37.97	37.68	37.52	37.22	37.06	37.08	36.96
17	25.78	25.84	25.32	25.62	28.67	26.97	26.40
18	29.68	29.62	29.62	31.89	31.89	31.91	31.83
19	29.36	29.29	29.29	22.72	22.69	22.68	22.66
20	31.89	31.89	31.89	14.08	14.08	14.08	14.08
21	22.72	22.69	22.69				
22	14.14	14.11	14.11				
SOMe	30.79	33.22	31.89	31.50	32.74	31.16	71.68
SMe	15.67	13.00	15.15	15.38	13.00	14.03	9.98
$SiMe_2$				−4.45/−4.68	−4.36/−4.58	−4.54/−4.72	−4.55/−4.84
Me_3				25.94	26.01	25.93	25.84
>C<				18.24	18.24	18.02	17.98

[a] Prostaglandin numbering.

spectra were obtained with Varian A-60, HA-100, and EM-360 instruments and with a Brucker WH-90 spectrometer in deuteriochloroform or carbon tetrachloride, with Me_4Si as the internal standard. Mass spectra were taken on an Atlas CH7 or CH4 instrument (CH7 was coupled with a Hewlett-Packard HP F&M Scientific Model 402 gas chromatograph with a 1 m × 2 mm 3% SE-30 column at ca. 170–230 °C). Combustion analyses were performed by our microanalytical laboratory, Bernhardt Mikroanalytisches Laboratorium, West Germany, or the microanalytical laboratory, Chemistry Department, Stanford University. Thin-layer chromatography (TLC) was carried out on Analtech (Uniplate) glass plates precoated with silica gel GF (250 μm) and on Whatman (KC-18) glass plates precoated with octadecylsilane. High pressure liquid chromatography (high pressure LC) was performed either on a Waters Associates Prep LC/System 500 or an in-house instrument, both utilizing silica gel columns and Waters Associates differential refractometers for detection. Vapor-phase chromatography (VPC) was performed on a Varian Series 1200 Aerograph, with a 4 ft 10% OV-101 column.

4-[(*tert*-Butyldimethylsilyl)oxy]cyclopent-2-en-1-ol (11). 3,5-Cyclopentene diol (10.0 g, 100 mmol) and imidazole (13.6 g, 200 mmol) were dissolved in 100 mL of DMF and cooled to 0 °C. *tert*-Butyldimethylchlorosilane (15.1 g, 100 mmol), dissolved in 25 mL of DMF, was then added, and the mixture was maintained at 0 °C for 1.5 h, at which time TLC analysis showed the absence of the diol. The mixture was allowed to warm to ambient temperature and was then poured into 800 mL of H_2O and extracted with hexane (2 × 150 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford 17.8 g of crude product. Preparative high pressure LC (3:1 hexane–ethyl acetate) gave the product **11** as an oil (7.1 g, 33%): IR (film) 3400 (OH), 2920 (CH) cm^{-1}; ^1H NMR δ 5.80 (s, 2 H), 4.90 (m, 2 H), 1.90 (m, 2 H), 0.90 (s, 9 H), 0.00 (s, 6 H). Anal. Calcd for $C_{11}H_{22}SiO_2$ (214.37): C, 61.63; H, 10.34. Found: C, 61.48; H, 9.92.

4-[(*tert*-Butyldimethylsilyl)oxy]cyclopent-2-en-1-one (2a).[30] Pyridinium chlorochromate (10.5 g, 49 mmol) and sodium acetate (2.7 g, 32.7 mmol) were suspended in 60 mL of dichloromethane. To this mixture, cooled to ca. 0 °C, was added a solution of the alcohol **11** in 25 mL of dichloromethane. The reaction was allowed to proceed at ambient temperature, aliquots were analyzed by TLC and VPC, and the reaction was complete after 45 min. The solvent was removed in vacuo, and the residue was triturated with diethyl ether (2 × 200 mL). The combined ethereal solution was filtered through 5 g of silica gel, and the solvent was removed in vacuo to give a crude product (7 g). High pressure LC (5:1 hexane–ethyl acetate) yielded pure **2a** (5.1 g, 74%) as a white semisolid: UV (methanol) λ_{max} 320 (ε 95); IR (film) 1720 cm^{-1}; ^1H NMR δ 7.40 (d, d, 1 H), 6.15 (d, d, 1 H), 4.95 (m, 1 H), 2.40 (4d, 2 H), 0.90 (s, 9 H), 0.00 (s, 6 H); MS (70 eV) *m/e* 212 (M^+). Anal. Calcd for $C_{11}H_{20}SiO_2$ (212.35): C, 62.21; H, 9.49. Found: C, 62.21; H, 9.50.

2α-[2-(Methylsulfinyl)-2-(methylthio)ethyl]-3β-(3β-hydroxydec-1-*cis*-enyl)cyclopentanone (19a) and 2α-[2-(Methylsulfinyl)-2-(methylthio)ethyl]-3β-(3α-hydroxydec-1-*cis*-enyl)cyclopentanone (19b). 1-Iododec-1-*cis*-en-3-ol[23] (1.22 g, 4.3 mmol) was dissolved in 10 mL of 2-methoxypropene, and the mixture was treated with phosphorus oxychloride (≤25 μL). When protection was complete, as judged by TLC (1.5 h), the mixture was treated with triethylamine (100 μL) and concentrated in vacuo. The residue was dissolved in hexane (20 mL) and treated at −78 °C with *n*-butyllithium (3.1 mL, 1.55 M, 4.75 mmol). Lithiation was followed by VPC, and when the reaction was complete (1.0 h), $CuI[P(OMe)_3]_2$ complex[3] (0.95 g, 2.16 mmol) in 50 mL of diethyl ether was added. Cuprate formation was followed by the Gilman test,[3] and when the reaction was complete (≤1 h), the mixture was treated with cyclopentenone (139 mg, 1.7 mmol) in 1 mL of diethyl ether via syringe. VPC analysis showed no residual cyclopentenone after 10 min. The mixture was treated with 1-(methylsulfinyl)-1-(methylthio)ethylene[20] (**18**) (340 mg, 2.5 mmol). After an additional 40 min at −78 °C, the reaction mixture was allowed to reach 0 °C and then quenched with an equal volume of 30% aqueous acetic acid. This two-phase mixture was stirred at ambient temperature for 2 h to remove the protecting group on the lower side chain. The two phases were separated; the organic phase was washed with 10% aqueous NH_4OH (to no color) and with brine, dried ($MgSO_4$), and concentrated in vacuo. Preparative high pressure LC (ethyl acetate) of the residue afforded pure **19a** (270 mg, 43%): IR (film) 3300 (OH), 2900 (CH), 1730 (C=O), 1040 (CO), 930 (S=O) cm^{-1}; ^1H NMR δ 5.5 (m, 2 H), 4.3 (m, 1 H), 4.0 (2 m, 1 H), 2.48 (s, 3 H, CH_3SO), 2.5 (m, 4 H), 2.18 (s, 3 H, CH_3S), 1.25 (m, 16 H), 0.90 (m, 3 H); ^{13}C NMR (see Table I); MS (70 eV) *m/e* 311 (M^+ − CH_3SO). Anal. Calcd for $C_{19}H_{34}O_3S_2$ (374.58): C, 60.92; H, 9.15. Found: C, 60.71; H, 8.82. Also isolated was pure **19b** (49 mg, 8%): IR (film) 3300, 2900, 1730, 1040 cm^{-1}; ^1H NMR δ 5.35 (m, 2 H), 4.35 (m, 1 H), 3.90 (d, 2 H), 3.40 (bs, 1 H, OH), 2.65 (s, 3 H, CH_3SO), 2.25 (m, 4 H), 2.15 (s, 3 H, CH_3S), 1.25 (m, 16 H), 0.90 (m, 3 H); ^{13}C NMR (see Table I); MS (70 eV) *m/e* 357 (M^+ − OH). Anal. Calcd for $C_{19}H_{34}O_3S_2$ (374.58): C, 60.92; H, 9.15. Found: C, 60.67; H, 8.76.

2α-[2-(Methylsulfinyl)-2-(methylthio)ethyl]-3β-(3α-hydroxydec-1-*trans*-enyl)cyclopentanone (20). To a solution of **19a** (40 mg, 0.11 mmol) in diethyl ether (20 mL) was added triethylamine (30 mg, 0.3 mmol). This mixture was treated via syringe with benzenesulfenyl chloride (29 mg, 0.2 mmol). When the reaction was complete as judged by TLC (1.5 h), the mixture was diluted with diethyl ether (20 mL), filtered, and concentrated

(30) This oxidation can be carried out also with manganese dioxide.[8a]

in vacuo. The residue was dissolved in methanol (20 mL) and treated with trimethyl phosphite (50 mg, 0.4 mmol). After 2 h, the reaction was complete as judged by TLC. The reaction mixture was concentrated in vacuo, and the residue was purified by high pressure LC (2:1 hexane–acetone) to give pure **20** (36 mg, 90%): IR (film) 3300, 2900, 1730 cm^{-1}; ^1H NMR δ 5.75 (m, 2 H), 4.0 (m, 2 H), 2.55 (s, 3 H, CH_3SO), 2.25 (m, 4 H), 2.20 (s, 3 H, CH_3S), 1.30 (m, 16 H), 0.90 (m, 3 H); ^{13}C NMR (see Table I); MS (70 eV) m/e 311 ($M^+ - CH_3SO$), 310 ($M^+ - CH_3SOH$). Anal. Calcd for $C_{19}H_{34}O_3S_2$ (374.58): C, 60.92; H, 9.15. Found: C, 60.80; H, 9.45.

2α-[2-(Methylsulfinyl)-2-(methylthio)ethyl]-3β-(3β-hydroxyoct-1-*cis*-enyl)-4α-[(*tert*-butyldimethylsilyl)oxy]-cyclopentanone (21a) and 2α-[2-(ethylsulfinyl)-2-(methylthio)ethyl]-3β-(3α-hydroxyoct-1-*cis*-enyl)-4α-[(*tert*-butyldimethylsilyl)oxy]cyclopentanone (21b). 1-Iodooct-1-*cis*-en-3-ol[3] (3.0 g, 11.8 mmol) was protected with 2-methoxypropene and lithiated in hexane (50 mL) with *n*-butyllithium (7.8 mL, 1.5 M, 12.5 mmol) (see above). Lithiation was complete after 30 min. To the organolithium solution (at −78 °C) was added the CuI-$[P(OMe)_3]_2$ complex (2.85 g, 6.5 mmol) dissolved in diethyl ether (250 mL). The mixture was maintained at −78 °C for 30 min at which time the Gilman test was negative. 4-[(*tert*-Butyldimethylsilyl)oxy]cyclopent-2-en-1-one (**2a**) (1.0 g, 4.7 mmol) in 5 mL of diethyl ether was added via syringe, and after 30 min 1-(methylsulfinyl)-1-(methylthio)ethylene (**18**) (1.6 g, 11.8 mmol) in 5 mL of diethyl ether was added via syringe. After 30 min, the reaction mixture was allowed to warm to 0 °C and was then quenched with an equal volume of 30% aqueous acetic acid. After workup as previously described, the mixture was purified by preparative high pressure LC (ethyl acetate) to give pure **21a** (1.0 g, 45%): IR ($CHCl_3$) 3400, 2920, 1740 cm^{-1}; ^1H NMR δ 5.65 (m, 1 H), 5.35 (m, 1 H), 4.15 (m, 1 H), 3.90 (m, 1 H), 3.30 (m, 1 H), 3.00 (bm, 1 H, OH), 2.40 (s, 3 H, CH_3SO), 2.30 (m, 3 H), 2.15 (s, 3 H, SCH_3), 1.30 (m, 8 H), 0.90 (m, 12 H), 0.00 (s, 6 H); ^{13}C NMR (see Table I); MS (70 eV) m/e 412 ($M^+ - CH_3SOH$). Anal. Calcd for $C_{23}H_{44}O_4SiS_2$ (476.82): C, 57.90; H, 9.30. Found: C, 57.76; H, 8.94. Pure **21b** was also isolated (0.18 g, 8%): IR($CHCl_3$) 3400, 2930, 1740 cm^{-1}; ^1H NMR δ 5.40 (m, 2 H), 4.25 (m, 2 H), 2.85 (m, 1 H), 2.65 (s, 3 H, CH_3SO), 2.30 (m, 3 H), 2.15 (s, 3 H, CH_3S), 1.90 (bs, 1 H, OH), 2.25 (m, 1 H), 1.30 (m, 7 H), 0.90 (m, 12 H), 0.00 (s, 6 H); ^{13}C NMR (see Table I); MS (70 eV) m/e 476 (M^+), 412 ($M^+ - CH_3SOH$). Anal. Calcd for $C_{23}H_{44}O_4SiS_2$ (476.82): C, 57.90; H, 9.30. Found: C, 57.81; H, 9.54.

2α-[2-(Methylsulfinyl)-2-(methylthio)ethyl]-3β-(3α-hydroxyoct-1-*trans*-enyl)-4α-[(*tert*-butyldimethylsilyl)-oxy]cyclopentanone (22). This *cis*-allylic alcohol **21a** (330 mg, 0.69 mmol), dissolved in 50 mL of diethyl ether, was treated at −10 °C with triethylamine (280 mg, 2.77 mmol) and then, dropwise, with benzenesulfenyl chloride (150 mg, 1.04 mmol). When the reaction was complete as judged by TLC (2 h), the reaction mixture was concentrated in vacuo, redissolved in 50 mL of methanol, and treated at ambient temperature with trimethyl phosphite (340 mg, 2.77 mmol). The reaction was complete after 3 h (as judged by TLC). The mixture was concentrated in vacuo, and the residue was purified by high pressure LC (2:1 hexane–acetone) to give pure **22** (245 mg, 74%): IR (film) 3400, 2940, 1735 cm^{-1}; ^1H NMR δ 5.65 (m, 2 H), 4.10 (m, 3 H), 2.55 (s, 3 H, CH_3SO), 2.35 (m, 4 H), 2.15 (s, 3 H, CH_3S), 1.25 (m, 10 H), 0.90 (m, 12 H), 0.00 (s, 6 H); ^{13}C NMR (see Table I); MS (70 eV) m/e 412 ($M^+ - CH_3SOH$). Anal. Calcd for $C_{23}H_{44}O_4SiS_2$ (476.82): C, 57.90; H, 9.30. Found: C, 57.50; H, 9.67.

2α-[2-(Methylsulfinyl)-2-(methylthio)ethyl]-3β-(3α-hydroxyoct-1-*trans*-enyl)-4α-[(*tert*-butyldimethylsilyl)-oxy]-1α-cyclopentanol (23). The ketone **22** (200 mg, 0.42 mmol), dissolved in 100 mL of THF, was cooled to −78 °C and treated via syringe with L-Selectride (0.46 mL, 1.0 M, 0.46 mmol). The reaction was complete after 5 min (as judged by TLC). The mixture was quenched with H_2O (10 mL), allowed to reach ambient temperature, and then extracted with ethyl acetate (3 × 50 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo to give the product **23** (190 mg, 95%): IR (film) 3400, 2920 cm^{-1}; ^1H NMR δ 5.55 (m, 2 H), 4.55 (m, 1 H), 4.00 (m, 2 H), 3.65 (m, 1 H), 2.55 (s, 3 H, CH_3SO), 2.35 (m, 4 H), 2.20 (s, 3 H, CH_3S), 1.25 (m, 10 H), 0.90 (m, 12 H), 0.00 (s, 6 H); ^{13}C NMR (see Table I); GC–MS (($Me_3Si)_2$ derivative) (70 eV) m/e 558 ($M^+ - CH_3SOH$). Anal. Calcd for $C_{23}H_{46}SiO_4S_2$ (478.84): C, 57.69; H, 9.68. Found: C, 57.57; H, 9.60.

(±)-$PGF_{2\alpha}$ (25). The dithioketal **23** (20 mg, 0.04 mmol), dissolved in 40 mL of THF, was treated at ambient temperature with 1.0 mL of 9 N HCl. The reaction was followed by TLC and was complete after 1 h. The mixture was diluted with H_2O (40 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo to give crude **24**.

To 40 mL of Me_2SO was added NaH (24 mg, 50% oil dispersion, 0.5 mmol). The mixture was placed in a 60 °C oil bath for 1 h and then cooled to ambient temperature. To this solution was added (4-carboxy-*n*-butyl)triphenylphosphonium bromide[24] (91 mg, 0.25 mmol). After 30 min, the previously prepared lactol **24**, dissolved in 20 mL of Me_2SO, was added to the ylide solution, and the mixture was maintained at 40–45 °C, while the course of the reaction was followed by TLC. After 2 h the reaction was complete, and the mixture was poured into 120 mL of water, acidified to pH 4, and extracted with ethyl acetate (5 × 50 mL). The combined organic phase was washed with H_2O (3 × 50 mL) and brine, and the organic phase was dried ($MgSO_4$) and concentrated in vacuo. High pressure LC (500:40:0.5 CH_2Cl_2–CH_3OH–HCOOH) of the residue gave **25** (9 mg, 63%). In another experiment (on a larger scale), crystallization from ethyl acetate–hexane gave pure (±)-$PGF_{2\alpha}$ (58%): mp 55–57 °C (lit.[26] mp 55–56 °C). Anal. Calcd for $C_{20}H_{34}O_5$ (354.47): C, 67.76; H, 9.67. Found: C, 68.02; H, 9.63.

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