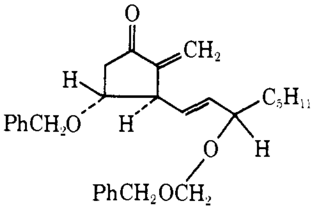
A Simple Total Synthesis of Prostaglandins from 4-Cumyloxy-2-cyclopentenone

Sir:

We have recently described a synthetic route to prostaglandins which utilizes the 2-methylene cyclopentanone **1** as a key intermediate.[1] The latter was synthetized via reaction of the kinetic enolate **2**, derived from the bromoketone **3**, with formaldehyde.



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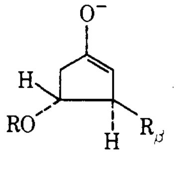

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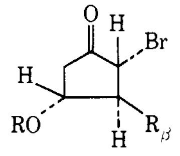

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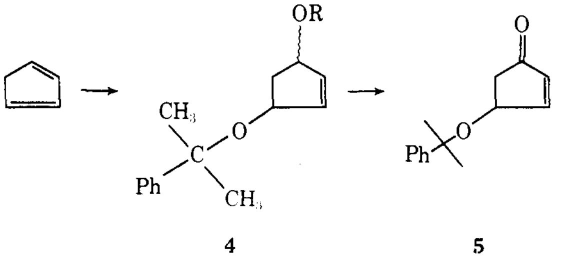
Chemically more complex enolates of the same regiostructure as **2** are, of course, formed via conjugate addition or organocuprates to suitably protected 4-hydroxy-2-cyclopentenones.[2] In spite of the very poor results reported in alkylating such enolates, even with reactive allylic halides,[3] we believed that they might yield to the unusual effectiveness of monomeric formaldehyde in the trapping of kinetic enolates.

We now report the successful completion of this approach to $PGF_{2\alpha}$ via the readily available[4] 4-cumyloxy-2-cyclopentenone (**5**). The latter undergoes conjugate additions in very good yields[4] and is easily obtainable from cyclopentadiene.[5] To a cold solution of 0.2 mol of cyclopentadiene, 0.1 mol of cumyl hydroperoxide,[6] and 0.11 mol of cupric acetate in 60 ml of acetic acid was added (40 min, under nitrogen) a cold solution of 0.11 mol of ferrous sulfate in 60 ml of water. Work-up, after 1 hr at room temperature, and rough distillation gave the crude acetates **4**, R = OAc. Hydrolysis (10% potassium hydroxide-methanol,[7] room temperature, overnight) to the epimeric alcohols **4**, R = H (chromatography on activity II alumina) and oxidation (Jones) gave the required cyclopentenone **5** in ∼48% overall yield from cumyl hydroperoxide.



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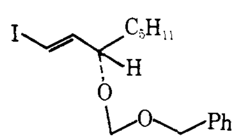
Protection of (+)-1-iodo-1-octen-3-ol[2b,8] ([α]D +10.0°) as its benzyloxymethyl ether was carried out by treatment with 1.2 equiv of benzyl chloromethyl ether (ethyldiisopropylamine, 10° to room temperature, overnight). The iodo ether **6** was thus obtained in 95% yield after silica chromatography ([α]D −132° (*c* 3.0, THF); ir 2900, 1620, 1170, 1100, 1040, 950, 740, 700 cm^{-1}; NMR δ 7.35 (5 H, s), 6.4 (1 H, dd, J = 14.5, 4.5 Hz), 6.2 (1 H, d, J = 14.5 Hz), 4.8-4.35 (4 H, m), 1.7-1.1 (8 H, m), 0.85 (3 H, t)).

The crucial 1:4 addition-formaldehyde trapping was studied extensively and, although we could not achieve the yields which we were able to obtain with **2**, we succeeded in defining conditions that reproducibly gave yields of 50-60% for the conversion of **5** to **7**.



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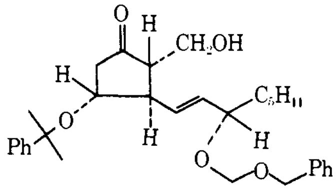

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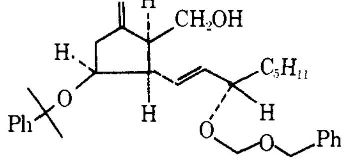

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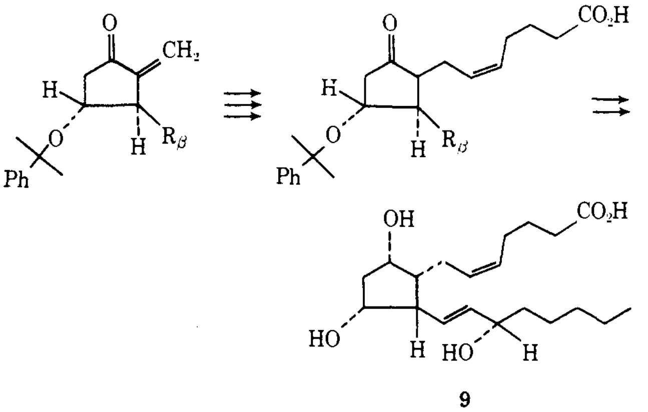
Addition of 3 mmol of the vinyl iodide **6** in ether to 6 mmol of 1.23 *M tert*-butyllithium (−78°, 2 hr under argon) was followed by addition of 1.5 mmol of tributylphosphine-cuprous iodide (dropwise 15 min, −50°; then an additional 45 min), addition of 1.5 mmol of **5** in ether (−78°, then 30 min at −40° and 30 min → −20°), followed by cooling to −78°, and addition of 6 ml of formaldehyde solution (∼1 *M* in ether) kept at −78°, and, after stirring for another 30 min (−78° → −50°), the reaction mixture was poured into saturated ammonium chloride solution. Washing of the ethereal extracts with ammonium chloride-ammonia buffer (pH 7.5-8.0)[9] and ammonium chloride solution gave after removal of excess side chain and other impurities (silica gel) a mixture of the required hydroxymethyl cyclopentanone **7** together with the mirror image of the 15-epi isomer **8** (**7**:**8** = ∼1.3:1).



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The remaining steps were carried out as previously described[1] with the benzyloxycyclopentanone analog of **7**[10] leading, after removal of the protecting groups with sodium-ammonia, to $PGF_{2\alpha}$ (**9**) and the mirror image of 15-epi $PGF_{2\alpha}$. Those were readily separated (as their methyl esters) by silica gel chromatography (ether-pentane) to give the methyl ester of (+)-PFG_2 [α]D +22.2° (*c* 1.70, THF), identical in all respects (ir, ^{1}H NMR, ^{13}C NMR, CI-MS, and TLC behavior) with the natural substance. Hydrolysis gave pure (+)-PGF_2, [α]D +22.7° (*c* 1.2, THF) (reported, +23.5°).

The value of formaldehyde as a trapping agent for certain enolates which undergo rapid equilibration under alkylation conditions is once again demonstrated. The relatively simple converging synthesis described here leads in eight steps from 4-cumyloxy-2-cyclopentenone (**5**) to (+)-PGF$_{2\alpha}$ and the enantioner of its 15-epimer in 17% overall yield.[11,12]

References and Notes

(1) G. Stork and M. Isobe, *J. Am. Chem. Soc.*, **97**, 4745 (1975).

(2) (a) C. J. Sih, P. Prince, R. Sood, R. G. Salomon, G. Peruzzotti, and M. Casey, *J. Am. Chem. Soc.*, **94**, 3643 (1973); (b) A. F. Kluge, K. G. Untch, and J. H. Fried, *ibid.*, **94**, 7827 (1972); (c) early experiments with 1,4 addition of vinyl cuprates to 4-acetoxy-2-(6-carbomethoxyhexyl)-2-cyclopentenone were carried out by Dr. K. Hattori at Columbia in 1967.

(3) Cf. footnote 10, ref 1; this is a special problem with the 4-oxygenated 2-cyclopentenones, largely because of the much greater acidity of the 5-methylene group caused by the inductive effect of the 4-alkoxy group (cf. A. A. Bothner-By and C. Sun, *J. Org. Chem.*, **32**, 492 (1967)).

(4) Cf. G. Stork, Q. Branca, H. W. Pinnick, J. Quick, and T. Takahashi, manuscript in preparation.

(5) This simplification of the method reported in ref 4 was initially studied by A. Mitra in this laboratory (cf. H. Haubenstock, P. G. Mennitt, and P. E. Butler, *J. Org. Chem.*, **35**, 3208 (1970).

(6) From Polysciences, Inc.

(7) The removal of the acetate can be carried out more cleanly, though less conveniently, with lithium aluminum hydride as described by Haubenstock et al. in a related case.

(8) The (±) form of this iodooctenol was first made by Dr. K. Hattori (ref 2c). The reactions described here with the optically active 1-iodo-1-octen-3-ol have also been carried out with the racemic substance, thus leading to (±)-PGE$_{2\alpha}$ and its 15-epimer.

(9) There appears to be some retroaldol loss of formaldehyde from **7** during work-up. This is minimized by repeated washing with the buffer (10 × 50 ml).

(10) The only (minor) differences involved the use of triethylamine in the elimination of the mesylate of **7** and the use of 2:1 (v/v) acetic acid–water at room temperature for 5 hr to hydrolyze the terminal ethoxyethyl protecting group. The spectra of the intermediates were very similar to those previously reported, with the replacement of the benzylic hydrogens signals of the previous series by the gem dimethyl 6 H singlet of the cumyloxy group at $\delta \sim 1.52$.

(11) Approximately 9% overall of pure (+)-PGF$_{2\alpha}$ and 7% of the 15-epi enantiomer from **5**.

(12) We thank the National Science Foundation and the National Institutes of Health for their support of this work.

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The Structure of Compounds Containing Linear and Tetrahedral Silicon–Mercury Bonds, a Uniquely Caged Lithium Ion

Sir:

We wish to report the first single-crystal X-ray diffraction studies of compounds containing silicon to mercury bonds. The cyclic compound 2,2,4,4,6,6,8,8-octamethyl-2,4,-6,8-tetrasila-1,5-mercuracyclooctane (I) is a centrosymmetric molecule containing two linear Si-Hg-Si moieties joined by methylene groups. The lithium tetrakis(dimethylphenylsilyl)mercurate (II) may be described as an isolated contact ion pair of crystallographic symmetry 2-C_2, in which the anion comprises a mercury tetrahedrally coordinated by four dimethylphenylsilyl groups with the two lithium cations entrapped in symmetry related cages comprised of the mercury, three silicon atoms, and five carbon atoms. The crystallographically required twofold axis passes through the mercury.

The structures of I and II are shown in Figures 1 and 2. One may contrast silicon-mercury bonds in the linear configuration and in the tetrahedral system. The Hg-Si distances are equivalent in the cyclic compound with a linear Si-Hg-Si system (178.7°) with an average distance of 2.503 Å, whereas in the tetrahedral system two clearly discernible distances are present at 2.493 and 2.549 Å with an average 2.521 Å distance. The distinctly different Hg-Si distances observed in $Li_2Hg(SiMe_2Ph)_4$ are a manifestation of the distortion caused by the lithium ion and may be accounted for by noting Si(1) interacts with two lithium cations, whereas Si(2) only interacts with a single lithium cation.

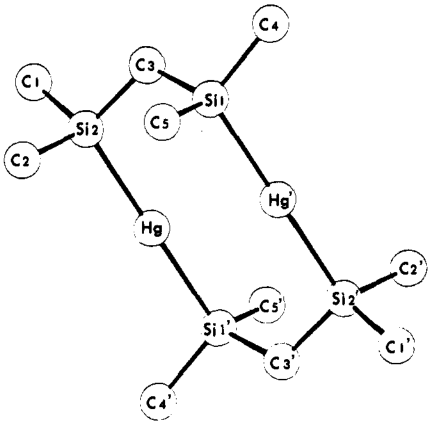

Figure 1. The skeletal structure of octamethyl-2,4,6,8-tetrasila-1,5-mercuracyclooctane.

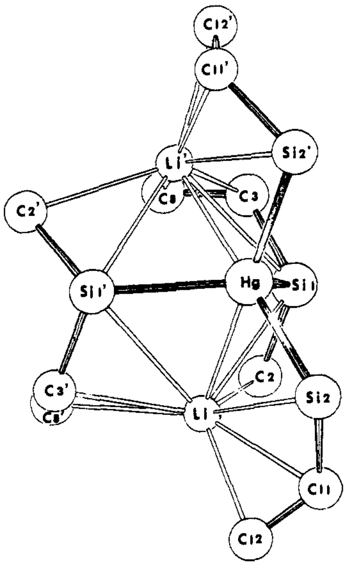

Figure 2. A partial structure of tetrakis(dimethylphenylsilyl)mercurate which shows the coordination of the lithium ions. Only the carbon atoms forming the cages around the lithium ions have been included for the sake of clarity. The C2 and C2′ carbons are methyl carbon atoms while all other carbons are phenyl carbon atoms.

These data, in conjunction with the earlier data reported on $^3J_{Hg-H}$ coupling,[1] support the relationship which has been proposed between the geometry surrounding mercury and $^3J_{Hg-H}$ which show a decrease from 43.5 to 27.0 to 19.0 Hz going from the linear sp hybridized mercury, to sp^2, to the sp^3 hybridized tetrahedral complex. This strongly supports the proposed trigonal coordination for the mercury atom in $Li[Hg(SiR_3)_3]$ species. Data for $^3J_{Hg-H}$ in the Me_2PhSi series of derivatives are given in Table I.

Figure 2 shows that the lithium ion is novelly encompassed in a cage composed of carbon, silicon, and mercury atoms. The lithium-carbon distances are in the range of 2.4–2.6 Å, slightly longer than lithium-carbon bonds in alkyl-lithium derivatives (2.18–2.30),[2] but similar to those observed in lithium-hydrocarbon ion pairs.[3] The silicon-lithium distances are 2.9–3.0 Å, again longer than the corresponding silicon-lithium bond distance observed in silyllithium derivatives (2.68 Å).[4] The lithium-mercury distance is 2.58 Å.

The most interesting feature of this system is the entrapment of the lithium ion by the silicon-carbon moieties of the anion which results in a "bare" lithium ion unlike those