As a final preliminary test of the trienal approach to systems such as **1b**, we selected as a target the diacid **21**, an intermediate recently prepared by Ireland in connection with synthetic studies on chlorothricolide.[8] The sequence is outlined in Scheme II.

The benzyloxy ester **14** (>95% *E,E* according to high-field ^{1}H NMR analysis) was prepared via condensation of 5-(benzyloxy)pentanal[9] with methyl (*E*)-(4-diethoxyphosphinyl)-2-butenoate in 84% yield.[10] Reduction with diisobutylaluminum hydride at −78 °C followed by Swern oxidation[4b] to the aldehyde, addition of 4,4-diethoxybutylmagnesium bromide, hydrolysis of the acetal with 50% aqueous oxalic acid, and treatment of the resultant δ-lactol with methyl 2-(triphenylphosphylidene)propionate afforded the triene ester **15** in 57% overall yield.[2a] Reduction of the hydroxyl-protected ester **16** and subsequent MnO_2 oxidation gave the desired trienal **17** in 82% yield (>90% *E,E,E* according to high-field ^{1}H NMR). Diels–Alder cyclization effected with diethylaluminum chloride at −78 to −23 °C led to a chromatographically separable 45:55 mixture of the bicyclic aldehydes **18** and **19** in 93% yield.[7] Interestingly, the *tert*-butyldimethylsilyl-protected aldehyde **17** gave over 95% of the α-isomer **18** (R′ = *t*-Bu(Me)$_2$Si) in greater than 90% yield under comparable conditions.

Correlation of aldehyde **18** with Ireland's diacid **21** was effected via reductive cleavage of the benzyl protecting group and oxidation of the resulting diol **20**. The material thus obtained was judged identical with a comparison sample according to TLC and high-field ^{1}H NMR analysis.[8]

The foregoing examples establish the practical feasibility of preparing hydronaphthalenes related to **1** via an intramolecular Diels–Alder strategy. Applications to appropriate natural products are currently under investigation.

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Supplementary Material Available: Spectral and physical data for compounds **3a**, **3b**, **4–7**, **11**, **12**, **14**, **15–18**, and **20** (7 pages). Ordering information is given on any current masthead page.

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Stereocontrolled Synthesis of Prostaglandins from Cyclopentadiene Monoepoxide[1]

Summary: Two complementary syntheses of prostaglandins from the same key intermediate **3**, available in four steps from cyclopentadiene monoepoxide, are described.

(1) A preliminary report of this work was presented at the 187th National Meeting, of the American Chemical Society St. Louis, MO, April 9, 1984; ORGN 7.

In one approach, a saturated α-chain is introduced via a 1,4-addition of an appropriately functionalized cyanocuprate reagent onto silyl enol ether **3**. The resulting prostanoid compound was converted into the bronchodilator 1-decarboxy-1-hydroxymethyl PGE_1, PGE_1, and $PGF_{1\alpha}$. The second approach involves the transformation of silyl enol ether **3** into the known prostanoid precursor **11** via selective addition of carbethoxycarbene and subsequent fluoride-induced ring opening of the resulting (silyloxy)cyclopropane carboxylate ester.

Sir: The past few years have witnessed an upsurge of interest in the general field of prostaglandin synthesis.[2] This high level of interest, sustained by the recognized therapeutic potential of these compounds, has more recently been stimulated by the unraveling of highly active and more selective analogues. Within this context, we report herein a new and stereocontrolled synthesis of prostaglandins, which offers maximum versatility for the attachment of a wide variety of side chains onto a preformed cyclopentane nucleus. The approach is primarily based on our observation of the high degree of regio- and stereoselectivity in the 1,4-addition of cyanocuprates to cyclic 1,3-diene monoepoxides.[3] Thus, conjugate addition of the cuprate reagent **1** onto cyclopentadiene monoepoxide, followed by cis-epoxidation and oxidation of the resulting allylic alcohol, provided the previously described[4] epoxy ketone **2**, which was quantitatively converted into its triethylsilyl enol ether **3**[5,6] by standard procedures. The introduction of the prostaglandin α-chain (or a readily convertible synthon for such a chain) onto this key intermediate was achieved by two different, albeit complementary, strategies, as illustrated in Scheme I.

In a "nucleophilic-type alkylation", a saturated α-chain was attached via a second conjugate addition of the cyanocuprate **4** derived from the timethylsilyl ether of 1-lithioheptan-7-ol.[7] After an ammonium chloride quench of the reaction mixture and subsequent hydrolysis of the resulting sily enol ether with a buffered potassium fluoride solution, an 80% yield of the 3-hydroxycyclopentanone derivative **5** was isolated.[8] The stereochemistry of the side chains in **5** was an 8:1 ratio of trans and cis epimers, respectively. The trans isomer was easily transformed into 1-decarboxy-1-hydroxymethyl PGE_1, **6**, by removal of the *tert*-butyldimethylsilyl group with aqueous HF in acetonitrile.[9] In addition, compound **5** could be selectively oxidized to the corresponding carboxylic acid with oxygen and platinum.[10] Deprotection of the C15 hydroxyl group as described before then yielded PGE_1.[11] Alternatively, stereoselective reduction of the C9 carbonyl of **5** with L-Selectride (Aldrich)[12] followed by selective oxidation of the primary alcohol and removal of the *tert*-butyldimethylsilyl group as indicated above provided $PGF_{1\alpha}$.[11]

In an "electrophilic-type alkylation", the enol ether derivative **7**, obtained in 90% overall yield by regiospecific reductive opening of the oxirane ring of **3** with $LiAlH_4$ and subsequent protection of the resulting 11-hydroxyl group, was cyclopropanated via the addition of carbethoxycarbene. It should be mentioned at this point that the direct introduction of a functionalized α-chain by regios-

(2) For recent reviews, see: (a) Bindra, J. S.; Bindra, R. "Prostaglandin Synthesis"; Academic Press: New York, 1977. (b) Mitra, A. "The Synthesis of Prostaglandins"; Wiley-Interscience: New York, 1977. (c) Nicolaou, K. C.; Gasic, G. P.; Barnette, W. E. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 293.

(3) For previous examples, see: (a) Marino, J. P.; Hatanaka, N. *J. Org. Chem.* **1979**, *44*, 4467. (b) Marino, J. P.; Abe, H. *Synthesis* **1980**, *11*, 872. (c) Marino, J. P.; Abe, H. *J. Org. Chem.* **1981**, *46*, 5379. (d) Marino, J. P.; Abe, H. *J. Am. Chem. Soc.* **1981**, *103*, 2907. (e) Marino, J. P.; Jaen, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3165.

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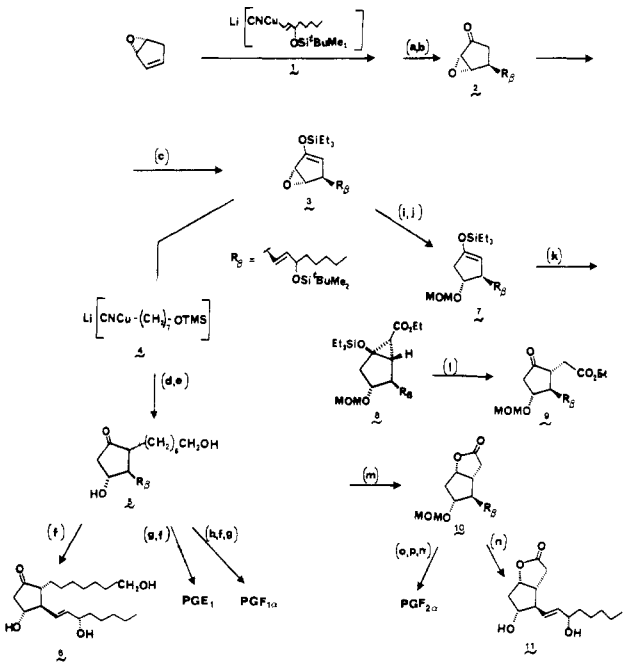
Scheme I[a]



[a] Reagents: (a) *t*-BuOOH, $VO(acac)_2$, PhH; (b) CrO_3·pyridine, CH_2Cl_2; (c) LDA, THF, −78 °C; then Et_3SiCl; (d) 4.0 equiv of 4, Et_2O, −78 °C → rt; (e) 1.3 equiv of KF, pH 7 phosphate buffer, EtOH; (f) HF, CH_3CN; (g) O_2, PtO_2, H_2O-acetone; (h) L-Selectride, THF, 0 °C; (i) $LiAlH_4$, Et_2O; (j) CH_3OCH_2Cl, *i*-Pr_2EtN, CH_2Cl_2; (k) EtO_2C-CHN_2, $CuSO_4$ (cat.), PhH, 90 °C; (l) Et_3NF, THF, rt; (m) PBPH, THF, −78 °C → rt; (n) 24% aqueous HBr, DME; (o) Dibal-H, CH_2Cl_2, −78 °C; (p) Na^+ [Ph_3P=CH-$(CH_2)_3CO_2^-$], PhH–Me_2SO, 75 °C.

pecific alkylation of **7** was unsuccessful and led to enolate equilibration and β-elimination of the protected 11-hydroxyl group.[13] The selective carbene addition onto the C8–C9 double bond, therefore, was devised as an indirect route, since such a reaction would render a (silyloxy)-substituted cyclopropane that could then be fragmented to generate the corresponding α-alkylated cyclopentanone.[14] Examination of models suggested that the carbene addition would preferentially take place from the α-side of the molecule (i.e., trans to the β-chain), setting up the correct stereochemistry at C8. Thus, reaction of **7** with ethyl diazoacetate in the presence of a catalytic amount of $CuSO_4$ gave **8** (70%) as a 4:1 mixture of exo and endo isomers, respectively.[15] Treatment of this mixture with triethylammonium fluoride effected selective desilylation of the triethylsilyl group and regiospecific opening of the cyclopropane ring to afford γ-keto ester **9** (95%) as the only product.[16] Reduction of the cyclopentanone carbonyl from the β-face of the molecule with lithium *cis,cis,trans*-perhydro-9b-boraphenalyl hydride (PBPH)[17] in THF at −78 °C, followed by warming of the resulting alkoxy ester solution, resulted in the formation of lactone **10** (80%). Removal of the protecting groups could be achieved simultaneously with 24% aqueous HBr in dimethoxyethane,[18] or, sequentially, by first removing the *tert*-butyldimethylsilyl group with 15% aqueous HF in acetonitrile[9] and then the methoxymethylene group with 5% HCl in aqueous THF. Chromatographic separation provided the known[19] lactone **11** (and its C15-epimer) in 30–40% overall yield from **2**. A conclusive proof of their structures was obtained by converting the hydroxy-protected lactone **10** into (±)-$PGF_{2\alpha}$[11] (and its C15-epimer) via reaction of the corresponding lactol with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide[20] and subsequent removal of the protecting groups.

In summary, the successful synthesis of PGE_1 and $PGF_{1\alpha}$ in less than ten steps from cyclopentadiene monoepoxide amply demonstrates the synthetic utility of the strategy involving a tandem 1,4-addition of cyanocuprates. The cyclopropanation approach, on the other hand, leads to a Corey lactone bearing a fully functionalized β-chain, which allows the synthesis of prostaglandins of the 2-series and many of their analogues.

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(4) Marino, J. P.; Kelly, M. G. *J. Org. Chem.* **1981**, *46*, 4389.
(5) The triethylsilyl (TES) enol ether exhibited greater stability than the corresponding trimethylsilyl (TMS) enol ether in the subsequent steps.
(6) Satisfactory spectral data (IR, ^1H and ^{13}C NMR, mass spectra) and elemental analyses were obtained for all new compounds.
(7) See ref 4 for a detailed procedure.
(8) The initial 1,4-adduct is a highly sensitive enol ether–allyl alcohol system, which should be rapidly hydrolyzed to the corresponding β-hydroxycyclopentanone in order to prevent elimination of the hydroxyl group.
(9) Newton, R. F.; Reynolds, D. P. *Tetrahedron Lett.* **1979**, 3981.
(10) Fried, J.; Sih, J. C. *Tetrahedron Lett.* **1973**, 3899.
(11) Our synthetic prostaglandins were spectroscopically (IR, 360-MHz ^1H NMR, and ^{13}C NMR spectra) compared to authentic samples kindly supplied by Dr. D. R. Morton of Upjohn.
(12) Brown, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 4100.
(13) Similar results have been reported by Davis, R.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 3755.
(14) For a review, see: Wenkert, E. *Acc. Chem. Res.* **1980** *13*, 27.
(15) Stereochemical assignments are based on 360-MHz ^1H NMR data of pure samples of each isomer. Also, their chemical structures have been unequivovally confirmed by independent conversion of each isomer into lactone **10**.
(16) For a detailed procedure, see: Reissig, H.-U.; Hirsch, E. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 813.
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Direct Formation of Organocopper Compounds by Oxidative Addition of Zerovalent Copper to Organic Halides

Summary: Mixing a solution of $CuI·P(Et)_3$ with a stoichiometric amount of lithium naphthalide in THF affords a zerovalent copper species that is sufficiently reactive to add to organic halides to give the corresponding organocopper compounds.

Sir: Reports over the past several years have demonstrated the very versatile utility of organocopper compounds in synthesis.[1,2] The vast majority of these reports have

