in preference to the desired mixed ligand complexes.[16] Thus, a difference in $SE_{C=C}$ of the olefinic substrates proved to play a crucial role in the construction of the key intermediate **1**. The exclusive production of the adduct **4** having endo stereochemistry,[17] as well as the efficient inhibitory effect of bis(diphenylphosphino)-ethane, provides definite evidence for the existence of the complex **1** in which **2** is acting as an endo bidentate ligand. With the chiral phosphine ligand present in the coordination sphere, two orientations of the substrates **2** and **3** are possible. Preferential formation or further reaction of one of these diastereomeric intermediates could lead to the observed enantioselective cyclobutane formation.

The exact factors which maintain the balance of the stability and the reactivity of the intermediary metal complexes, and which control the reaction course, remain to be elucidated. Attempts to characterize the reactive intermediates by physical methods are now in progress.

(16) Cyclopropene and 1-methylcyclopropene containing the extraordinarily high $SE_{C=C}$ (26 kcal/mol) polymerized violently under the present catalytic conditions (even at −60°).

(17) The major dimer of **2** has an endo,trans,exo structure.[2e]

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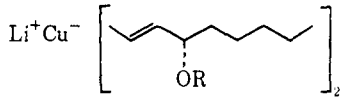
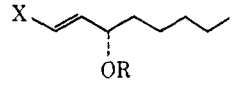
Total Synthesis of Prostaglandins. IV.[1] A Completely Stereospecific Synthesis of Prostaglandin E_1

Sir:

In a previous communication[2] we disclosed a concise novel route for the synthesis of prostaglandin E_1 (PGE_1, **8**) in its naturally occurring form. The prostanoic acid nucleus was constructed *via* conjugate addition of the cuprate **1a**, derived from (*S*)-*trans*-3-(1-ethoxyethoxy)-1-iodo-1-octene (**2b**), to (±)-2-(6-carboethoxyhexyl)-4-(2-tetrahydropyranyloxy)-2-cyclopenten-1-one (ethyl ester corresponding to **3b**). Since the attack by **1a** proceeded virtually exclusively from the least hindered side of **3b**, the configuration of the alkoxy function at C-4 in **3** is therefore of the utmost importance in dictating the eventual stereochemistry of the prostanoic acid skeleton at C-8 and C-12. We herein record an efficient method for the preparation of 2-(6-carbomethoxyhexyl)-4(*R*)-hydroxy-2-cyclopenten-1-one (**3a**)[3] and a refined procedure for the synthesis of (*S*)-*trans*-3-hydroxy-1-iodo-1-octene (**2a**).[4] The assembly of these two synthons[5] thus constitutes a completely stereospecific synthesis of PGE_1 (**8**).



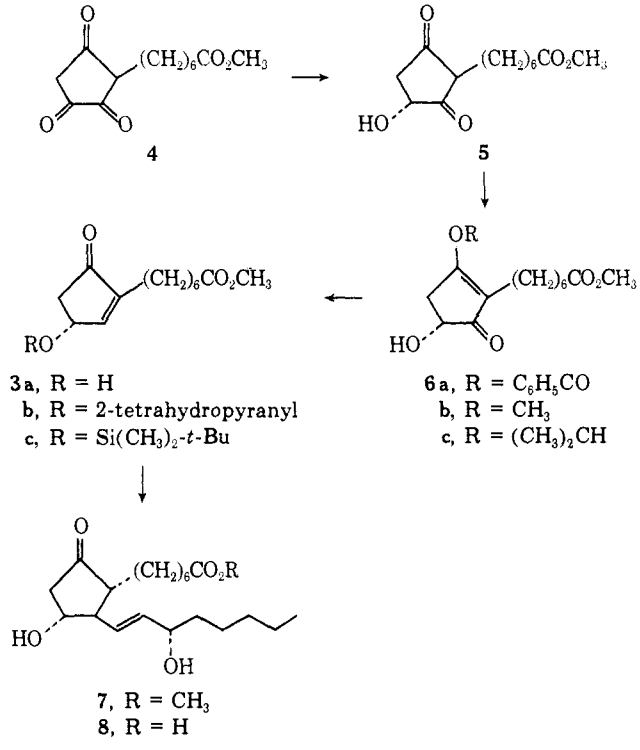
1a, R = $CH(CH_3)OCH_2CH_3$
b, R = $Si(CH_3)_2$-*t*-Bu



2a, X = I; R = H
b, X = I; R = $CH(CH_3)OCH_2CH_3$
c, X = I; R = $Si(CH_3)_2$-*t*-Bu
d, X = Li; R = $Si(CH_3)_2$-*t*-Bu

The scheme adopted for the preparation of the key intermediate **3**[6] and its reaction with the cuprate reagent **1** is summarized in Scheme I. The readily available 2-(6-carbomethoxyhexyl)cyclopentane-1,3,4-trione[7] (**4**) was best converted to 2-(6-carbomethoxyhexyl)-4(*R*)-hydroxycyclopentane-1,3-dione (**5**) by microbial reduction. A wide variety of microorganisms was found to be capable of performing the asymmetric reduction of **4** to **5**; the most suitable of these microbes was *Dipodascus uninucleatus* which gave completely stereospecific reduction to the 4(*R*) alcohol **5**. Exposure of 1 g of **4**, mp 79–81°, to this organism for 24 hr in a soybean–glucose medium gave 750 mg of **5**:[8] mp 89–91°; uv max (CH_3OH) 272 nm (ε 23,500); $[\alpha]^{24}D$ +16.1° (*c* 0.76, CH_3OH); CD (*C* 1.61 × 10^{-5}, CH_3OH),

Scheme I



3a, R = H
b, R = 2-tetrahydropyranyl
c, R = $Si(CH_3)_2$-*t*-Bu

6a, R = C_6H_5CO
b, R = CH_3
c, R = $(CH_3)_2CH$

7, R = CH_3
8, R = H

(1) Paper III of this series: C. J. Sih, R. G. Salomon, P. Price, R. Sood, and G. Peruzzotti, *Tetrahedron Lett.*, 2435 (1972).

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

(3) Compound **3a** has been synthesized previously as the racemic modification: (a) L. Heslinga, M. van Gorkom, and D. A. van Dorp, *Recl. Trav. Chim. Pays-Bas*, **87**, 1421 (1968); see also F. S. Alvarez, D. Wren, and A. Prince, *J. Amer. Chem. Soc.*, **94**, 7823 (1972); (b) C. J. Sih, R. G. Salomon, P. Price, G. Peruzzotti, and R. Sood, *Chem. Commun.*, 240 (1972); (c) R. Pappo and P. W. Collins, *Tetrahedron Lett.*, 2627 (1972).

(4) The procedure for the preparation of hydroxyvinyl iodide **2a** reported herein is a variant of a previously described procedure (ref 2). An alternate synthesis of **2a** has been published: (a) E. J. Corey and D. J. Beams, *J. Amer. Chem. Soc.*, **94**, 7210 (1972); (b) for the resolution of **2a**, see A. F. Kluge, K. G. Untch, and J. H. Fried, *ibid.*, **94**, 7827 (1972)].

(5) E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967).

(6) The approach described in this communication parallels that of Pappo and Collins.[3c]

(7) Prepared in 75–80% yield by the sodium ethoxide catalyzed condensation of methyl 9-ketodecanoate with ethyl oxalate; *cf.* J. Katsube and M. Matsui, *Agr. Biol. Chem.*, **33**, 1078 (1969). In turn 9-ketodecanoic acid was prepared in 95% yield from 8-carbomethoxyoctanoic acid *via* condensation of the corresponding acid chloride with ethoxymagnesiomalonic ester; *cf.* R. E. Bowman, *J. Chem. Soc.*, 322 (1950).

(8) Satisfactory infrared, nuclear magnetic resonance, and mass spectra were obtained.

22°; $[\theta]_{281}$ −85,000; $[\theta]_{262}$ +87,000. Although less satisfactory, partial asymmetric catalytic hydrogenation of **4** could be accomplished using a soluble rhodium catalyst with chiral phosphine ligands. Hydrogenation of **4** (4 g) in the presence of (1,5-cyclooctadiene)-bis(*o*-anisylcyclohexylmethylphosphine)rhodium(I) tetrafluoroborate[9] and triethylamine (1 equiv) in methanol under 1 atm of hydrogen gave, by direct crystallization, 1.7 g of **5**: uv max (CH_3OH) 272 nm (ε 23,500); the CD spectrum ($[\theta]_{281}$ −58,000; $[\theta]_{262}$ +60,000) indicated this product to be *ca.* 68% optically pure. Unfortunately, the mother liquor exhibited no optical activity.

Two methods were devised for the transformation of **5** into **3a** without racemization.[10] Reaction of **5** with triethylamine and 0.95 equiv of benzoyl chloride at −15° afforded the enol benzoate **6a**[8] (70%)[11] as an oil: uv max (CH_3OH) 241 nm (ε 20,100); $[\alpha]^{24}D$ +35.0° (*c* 2.0, $CHCl_3$). Reduction of **6a** by treatment with excess sodium bis(2-methoxyethoxy)aluminum hydride in tetrahydrofuran at −78°, followed by acidic hydrolysis (HOAc–H_2O 75:25, 37°, 26 hr), gave **3a** (60%): mp 60–61°; $[\alpha]^{24}D$ +17.8° (*c* 0.49, CH_3OH); CD (*C* 1.37 × 10^{-4}, CH_3OH), 22°; $[\theta]_{321}$ −9900; uv max (CH_3OH) 222 nm (ε 8200). In the alternate approach **5** was alkylated by refluxing with isopropyl iodide and K_2CO_3 in acetone for 16 hr to give the isopropyl enol ether **6c**[8] (53% yield by direct crystallization):[12] mp 60–62°; $[\alpha]^{24}D$ +35.1° (*c* 1.02, CH_3OH); uv max (CH_3OH) 259 nm (ε 20,600). Reduction with sodium bis(2-methoxyethoxy)aluminum hydride in tetrahydrofuran at −78°, followed by acidic hydrolysis (HCl–H_2O, pH 2.5, 25°, 1–2 hr), gave **3a** (60%): mp 60–61°; $[\alpha]^{24}D$ +17.6° (*c* 0.71, CH_3OH); uv max (CH_3OH) 222 nm (ε 8400).

The following modified hydroalumination procedure[13] was employed for the synthesis of iodide **2a**. Triisobutylaluminum (1.5 equiv) was added to (3*S*)-1-octyn-3-ol[14] in heptane to complex the alcohol function; diisobutylaluminum hydride (1 equiv) was then added, and the reaction mixture was heated at 50–55° for 2 hr. After treatment with iodine in tetrahydrofuran at −50° and acidic work-up, the small amount of saturated alkyl iodide by-product was removed by heating (15 hr, 80–85°) with triethylamine. The crude iodide **2a** was purified by chromatography and vacuum distillation to afford a colorless liquid;[8,15] bp 70° (0.02 mm), $[\alpha]^{24}D$ +9.52° (*c* 1.56, CH_3OH).

The iodo alcohol **2a**, protected as the *tert*-butyldimethylsilyl ether **2c**,[16] was treated with lithium powder in ether to give the vinyllithium reagent **2d** (>60% yield by the benzophenone method[4a]), which was added to 0.5 equiv of tri-*n*-butylphosphine–copper(I) iodide complex[17] to generate the cuprate **1b**. Protection of **3a** as the *tert*-butyldimethylsilyl ether **3c** and reaction with 1 equiv of cuprate **1b** (−15°, 0.5 hr) gave, after acidic hydrolysis of the protecting groups[16] and chromatography, PGE_1 methyl ester[18] (**7**, 65–70% yield based on **3a**). Hydrolysis of the methyl ester was effected by exposure of **7** to *Rhizopus oryzae* to yield PGE_1,[18] **8** (95% yield), mp 115–116°, $[\alpha]^{24}D$ −54° (*c*, 0.7 THF). The synthetic product was found to be identical (infrared, nuclear magnetic resonance, and mass spectra) with an authentic specimen[19] of natural PGE_1.

This short synthetic route (four integral steps from trione ester **4**) leads to natural PGE_1 in overall yields of 15% (not optimized). Further refinements of this approach and its extension to PGE_2 are currently in progress.[20,21]

(9) W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, *Chem. Commun.*, 10 (1972). We thank Dr. W. S. Knowles of the Monsanto Co. for a generous supply of this catalyst.

(10) Attempts to convert **5** into the methyl enol ether **6b** by refluxing with 2,2-dimethoxypropane and an acid catalyst as described by R. Pappo, P. Collins, and C. Jung, *Ann. N. Y. Acad. Sci.*, **180**, 64 (1971), gave only totally racemic material.

(11) The major by-product (20%) was 2-(6-carbomethoxyhexyl)-4(*R*)-benzoyloxycyclopentane-1,3-dione.

(12) Two isomeric isopropyl enol ethers were formed in the reaction, but only the desired isomer was crystalline.

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

(14) J. Fried, C. Lin, M. Mehra, W. Kao, and P. Dalven, *Ann. N. Y. Acad. Sci.*, **180**, 38 (1971).

(15) The yield from (3*S*)-1-octyn-3-ol varied from 40 to 50%. Unreacted octynol (25–30%) could be recovered by fractional distillation.

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

(17) G. B. Kaufman and L. A. Teter, *Inorg. Syn.*, 7, 9 (1963).

(18) No stereoisomeric products were detected, thus indicating (1) the exclusive addition of the cuprate **1b** in a trans fashion to the C-4 substituent of **3c** and (2) the optical purity of the synthetic intermediates.

(19) C. Takeguchi, E. Kohno, and C. J. Sih, *Biochemistry*, **10**, 2372 (1971).

(20) This investigation was supported in part by research grants from the Wisconsin Alumni Research Foundation and the National Institutes of Health (AM-4874 and AM-9688).

(21) NOTE ADDED IN PROOF. The conversion of **5** to **3a** has now been attained in 60% yield by a modified procedure, thus raising the overall yield of *nat*-PGE_1 to *ca.* 30% from **4** without chromatographic purification of intermediates. This work will be reported in detail at a later date.

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Stable Free Radicals. XII. Direct and Sensitized Nitronyl Nitroxide Photochemistry in Aprotic Solvent

Sir:

During the course of studies of nitronyl nitroxides,[1] nitroxide radical impurities were encountered with unusually large nitrogen coupling, a^N = ~25 G (three esr lines). These impurities were found to be formed by room light during tlc separations. Although a competing photochemical reaction of the nitronyl nitroxide **1** predominated in water,[2] irradiation in aprotic solvents yielded the new nitroxide as the major radical product. We describe here the course of this reaction and outline preliminary experiments which document the expected ability of triplet sensitizers to effect doublet–doublet excitation of organic radicals.

Degassed pentane solutions 2.8 × 10^{-3} *M* in **1** were irradiated with >410-nm light at 20° with a 300-W projector. The combined solutions from five runs (150 mg of **1**) were evaporated at −78° and purified by tlc at 4° to give two new radicals. The less stable of these, **5**, had a well-resolved 51-line esr spectrum (C_6H_6), $a^{N\text{-}1}$ = 12.25 G, $a^{N\text{-}2}$ = 1.72 G, a^H (6 H) = 0.50 G, g = 2.0046, similar to that of the structurally related nitroxide **6**, $a^{N\text{-}1}$ = 11.61 G, $a^{N\text{-}2}$ = 1.67 G,

(1) E. F. Ullman, J. H. Osiecki, D. G. B. Boocock, and R. Darcy, *J. Amer. Chem. Soc.*, **94**, 7049 (1972).

(2) L. Call and E. F. Ullman, *Tetrahedron Lett.*, in press.