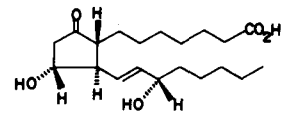
Chiral Synthesis of Prostaglandins (PGE_1) from D-Glyceraldehyde

Sir:

We report here the synthesis of a typical prostaglandin PGE_1 (**1**), in which the correct absolute configuration is produced from D-glyceraldehyde via **2** which serves to control the chirality of the rest of the PGE_1 molecule by means of a remarkably effective kinetic solution.



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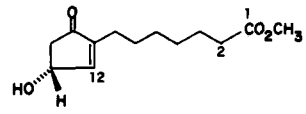
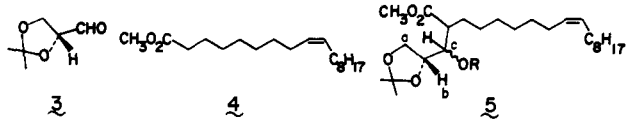


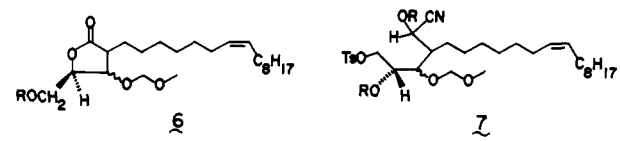
2

We first describe the construction of **2** from the readily available isopropylidene D-glyceraldehyde (**3**)[1] and methyl oleate (**4**). Addition of **3** ($[\alpha]^{25}_D$ 66.4°; c = 80.9 in benzene) in tetrahydrofuran (THF) to the anion of **4** (lithium diisopropylamide in THF–10% hexamethylphosphoramide, −78 °C) gave, after 2 h, the aldol **5**,[2] R = H, in 76% yield: IR 3550, 1750, 1725, cm^{-1}; NMR δ 0.9 (bt, 3 H), 3.72, 3.73 (s, 3 H), 3.8–4.15 (m, 4 H (a, b, c)), 5.35 (bt J = 4.5 Hz, olefinic, 2 H). The choice of methyl oleate for this addition reflects the fact that its double bond ends up in the aldol **5** at the proper place to be a latent carboxyl of the eventual heptanoic acid chain. Protection of the secondary hydroxyl group (excess chloromethyl methyl ether in diisopropylethylamine (0 °C, 1 h → room temperature, 8 h) gave **5**, R = CH_3OCH_2–, in 86% yield: IR 1750 cm^{-1}; NMR δ 3.34 (s, 3 H, ether OCH_3), 3.70 (s, 3 H, ester OCH_3), 4.68, 4.71 (s, 2 H, OCH_2O). We note here that the hydroxyl of **5**, R = H, was changed into an acetal of



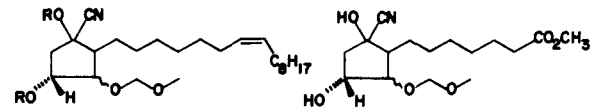
3 **4** **5**

formaldehyde because the protecting group has to be stable to the acid conditions involved in the removal of isopropylidene and ethoxyethyl groups (**5** → **6**; **8** → **9**) and to the introduction of the latter (**7**, OH → **7**,OR). It also needs to be a better departing group than hydroxyl (vide infra). Removal of the isopropylidene group and lactonization (10% aqueous sulfuric acid–THF, room temperature, 48 h) gave the γ-lactone **6**, R = H, (IR 1780 cm^{-1}) in 72% yield. Conversion to the tosylate **6**, R = tosyl (1.5 equiv of tosyl chloride in pyridine, 12 h, 0 °C to room temperature; 73% yield) was followed by transformation via the cyclic hemiacetal (1.1 equiv of diisobutylaluminum hydride in toluene, −40 °C, 1 h) to the hydroxy aldehyde cyanohydrin **7**, R = H (excess hydrogen cyanide in



6 **7**

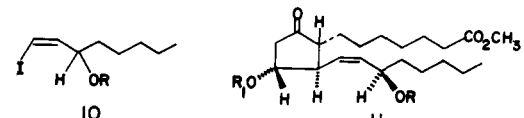
ethanol–catalytic amount of concentrated ammonia, 1 h, 0 °C; neutralization of ammonia before workup), in 65% yield. Cyclization to the cyclopentane ring of **8** was carried out in 85% yield after formation of **7** R = 1-ethoxyethyl (ethyl vinyl ether, concentrated hydrochloric acid catalyst, 0 °C, 9 h, 83% yield) by refluxing 6 h in benzene with 3 equiv of sodium hexamethyldisilazane. This application of the protected cyanohydrin as acyl carbanion equivalent[3] illustrates two special advantages of this process for the present construction: The stability to oxidation is important in the transformation of **8** to **9**, and the stability of cyanohydrins to mild acid keeps the latent aldol systems (cf. **9**) protected until the final mild base step. Oxidation of the double bond of **8**, R = 1-ethoxyethyl, to a carboxylic acid with sodium periodate–potassium permanganate,[4] removal of the ethoxyethyl protecting groups with aqueous acid, and esterification with diazomethane, then gave the cyanohydrin ester **9** in 46% yield from **8**.



8 **9**

The stage was now set for the generation of the desired methyl ester of 3-(*R*)-hydroxy-5-oxo-1-cyclopentene-1-heptanoic acid (**2**). Treatment of **9** in 2:1 ether–THF with 2% sodium hydroxide at 0 °C for 30 min, followed by acidification with ice-cold 0.1 N hydrochloric acid, gave, after chromatography on silica gel, crystalline **2** (80% yield), recrystallized from ethyl acetate: mp 60–60.5 °C,[5] $[\alpha]^{25}_D$ +15.5° (c = 1.12, MeOH); CD_{321nm} −9150° (C = 2.65 × 10^{-4} in MeOH, 25 °C); IR ($CDCl_3$), 1750, 1725, 1660 cm^{-1}; ^{13}C NMR 51.47, 174.3, 33.89, 24.70, 28.77, 28.91, 24.30, 27.25, 147.0, 207.1, 44.80, 68.03, 157.3 (OCH_3 and C_1···C_{12}, respectively).

At this point, the problems involved in an enantiospecific synthesis of PGE_1 can be considered solved because of the remarkable observation by Kluge, Untch, and Fried[6] that the (+) component of the (±)-cyclopentenone **2**, as its 2-methoxypropyl ether, reacts considerably more rapidly than its antipode with the divinylcuprate derived from the (*R*) isomer of the cis vinyl iodide **10**: the ratio of the desired product **11** to its C_{11} epimer was 86:14. Our construction of **11** involves the converse



10 **11**

of the above experiment: Reaction of the (+)-cyclopentenone, **2**, with the divinylcuprate from the (±)-vinyl iodide, **10**.[6] As a first approximation, the relevant transition states involved in our construction are either identical (reaction of (+)-**2** with (*R*)-**10**) or enantiomeric ((+)-**2** with (*S*)-**10**) with the ones involved in the Syntex experiments.[6] We believe that there is actually a significant advantage to the particular version used here in that there is none of the wrong enantiomer of **2** present to react with the excess divinylcuprate after the correct one has been used up. We, therefore, expected that a ratio at least as favorable as 86:14, and probably better, would be obtained. Indeed, reaction of the tetrahydropyranyl ether of **2** with 3 equiv of the cuprate from **10**, R = 2-methoxyisopropyl, essentially as described for the related case gave, after removal of the protecting groups, the methyl ester of 13-*cis*-15(*R*)-PGE_1, **11**, R,R_1 = H, $[\alpha]^{25}_D$ −75° (c = 0.357 in MeOH); clearly identical with the previously described substance.[6-8] *We were unable to detect the unwanted isomer.*[9] Completion of the synthesis of PGE_1 requires the correction of the 13-*cis*-15(*R*) side chain of **11** to the 13-*trans*-15(*S*) arrangement of **1**. This has been described previously.[7,10]

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

References and Notes

(1) E. Baer and H. O. L. Fischer, *J. Am. Chem. Soc.*, **61**, 761 (1939).

(2) The various substances referred to in the text were purified by chromatography on silica gel, unless otherwise noted, using the following elution mixtures: **5**, R = H, 25% ether–hexane; 5, R = methoxymethyl, 15% ether–hexane; **6**, R = H, 50% ether–benzene; **6**, R = Tos, 30% ether–benzene; **7**, R = H, 15% ethyl acetate–benzene; **7**, R = 1-ethoxyethyl, 20% ether–hexane; **8**, R = 1-ethoxyethyl, 17% ether–hexane; **9**, 25% ether–benzene; **10** (basic alumina), 50% ether–hexane; **11**, 5:1 → 3:1 ethyl acetate–hexane. All of the compounds referred to gave spectral data

(IR, NMR) in agreement with the expected structures.
(3) G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **92**, 5286 (1971).
(4) R. U. Lemieux and E. Von Rudloff, *Can. J. Chem.*, **33**, 1701, 1710 (1955).
(5) This substance has previously been made by a combination of chemical and microbiological methods: C. J. Sih, R. G. Salomon, P. Price, R. Sood, and G. Peruzzotti, *J. Am. Chem. Soc.*, **97**, 857 (1975). Reported: mp 60–61 °C, $[\alpha]^{24}_D$ +17.2.
(6) A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 9256 (1972). See ref 7, footnote 13a.
(7) J. G. Miller, W. Kurz, K. G. Untch, and G. Stork, *J. Am. Chem. Soc.*, **96**, 6774 (1974).
(8) ^{13}C NMR 214.9, 174.0, 136.6, 133.0, 71.06, 66.83, 55.17, 51.36, 49.43, 46.49, 36.81, 33.92, 31.80, 29.36, 28.88, 27.78, 26.60, 25.16, 24.81, 22.61, 14.01; IR (neat) 3600–3100, 2950, 1740, 1720, 1475, 1450 cm^{-1}; CD ($c = 1.218 \times 10^{-3}$, methanol, 25 °C, 296 nm) 10 600. CI-MS 351 $(M + 1)^+$, 333 $(M + 1 - H_2O)^+$; R_f 0.11 (hexane:ethyl acetate, 55:45); HPLC (retention time 62–80 min, on Porasil-A, 2 × 3/8 in. × 2 ft) in hexane–ethyl acetate 1:2, 3 ml/min.
(9) We are indebted to R. Davis and K. Untch (Syntex Research) for repeating this conjugate addition. Under conditions which had given them a ratio of 86:14 in favor of the desired isomer, they were unable to detect *any* of the unwanted isomer by direct comparison (TLC, NMR, HPLC on the silylated product). As little as 0.5% of the unwanted isomer would have been detected.
(10) For a previous chiral synthesis of a prostaglandin (PGA_2), see G. Stork and S. Raucher, *J. Am. Chem. Soc.*, **98**, 1583 (1976).

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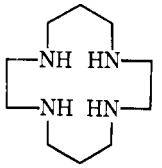
Homolytic Photochemical Processes in an Organo-Cobalt Complex Containing Saturated Ligands and the Nature of the Cobalt-Carbon Bond[1]

Sir:

Photoredox processes in most cobalt(III) complexes are stimulated by the absorption of radiation of energies comparable to the energies of ligand to metal charge transfer absorption bands.[2] For most cobalt complexes this means that the homolytic cleavage of metal ligand bonds is a process characteristic of ultraviolet or high energy visible excitations. In contrast, homolytic processes are known to occur throughout the visible absorption region for most organo-cobalt complexes.[3-7] Unfortunately, the assignment of electronic transitions for most organo-cobalt complexes is ambiguous since these complexes exhibit intense electronic transitions probably mediated by unsaturated equatorial ligands. Thus it has not been possible to critically explore the relationship of homolytic processes to the nature of the absorption bands irradiated. We have therefore undertaken a photochemical investigation of $Co([14]aneN_4)(OH_2)CH_3^{2+}$.[8] This complex



$[14]aneN_4$

has an absorption spectrum[9] (Figure 1) very similar to that of $Co(NH_3)_6^{3+}$, with charge transfer and other strongly allowed absorptions confined to the ultraviolet and with two weakly forbidden transitions in the visible–near-ultraviolet region.

We have been able to detect only one photochemical process (eq 1)

$$Co([14]aneN_4)(OH_2)CH_3^{2+} + h\nu \rightarrow Co^{II}([14]aneN_4) + CH_3 + H_2O \quad (1)$$

following irradiation of any absorption band of $Co([14]aneN_4)(OH_2)CH_3^{2+}$. The quantum yield for this homolytic process is essentially independent of excition wavelength ($\Phi = 0.30 \pm 0.04$). The contrasts to the photochemical behavior of acidopentaamminecobalt(III) complexes are striking: (1) homolysis is induced by irradiations of absorption bands much lower in energy than the charge transfer absorptions; (2) homolytic cleavage of the $Co-CH_3$ bond requires less energy than homolytic cleavage of most $Co^{III}-X^-$ bonds;[2] (3) most acidopentaammine complexes exhibit strongly wavelength dependent photochemistry;[2] (4) there is no distinct absorption feature which can be attributed to a $CH_3^- \rightarrow Co(III)$ transition (note: $Co([14]aneN_4)(OH_2)_2^{3+}$ has a charge transfer band at about 200 nm).

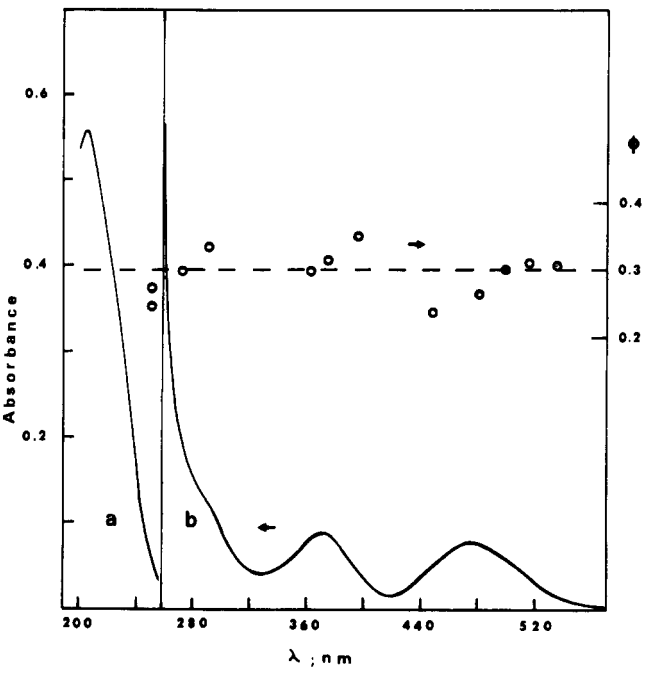


Figure 1. Absorption spectrum and wavelength dependence of homolysis quantum yield, ϕ, for $Co([14]aneN_4)(OH_2)CH_3^{2+}$: curve a 2.35×10^{-5} M $Co([14]aneN_4)(OH_2)CH_3^{2+}$ in 10^{-3} M $HClO_4$; curve b, 9.78×10^{-4} M $Co([14]aneN_4)(OH_2)CH_3^{2+}$ in 10^{-3} M $HClO_4$. Dashed line represents average value of quantum yields.

The spectroscopy and the photochemistry of $Co([14]aneN_4(OH_2)CH_3^{2+}$ combine to provide new and unique information about the nature of the cobalt-methyl bond. To illustrate this we first designate the $Co-CH_3$ bonding orbital by ψ_B and the $Co-CH_3$ antibonding orbital by ψ_{AB}. In the approximate C_{4v} symmetry of the complex the $\psi_B \rightarrow \psi_{AB}$ transition is strongly allowed. From the absorption spectrum it is evident that the difference in orbital energies (i.e., not including the Franck-Condon contributions to the optical transitions) is $E_0(\psi_{AB}) - E_0(\psi_B) = 3.4\ \mu m^{-1}$. The bond energy is given by the energy threshold for process 1 and we find that $E_{th} \leq 1.8\ \mu m^{-1}$. Consequently $E_0(\psi_{AB}) - E_0(\psi_B) \gg E_{th}$, no doubt owing to a relatively large contribution of the exchange integral[10] to the transition energy for the cobalt complexes. For more conventional complexes of cobalt(III) (e.g., acidopentammines), the close correspondence of $E_0(\psi_{AB}) - E_0(\psi_B)$ to E_{th} suggests that contributions of the exchange integral are small compared to those of the Coulomb integral. This contrast between halo and methyl complexes is consistent with the much larger electron affinity of $\cdot X$[11] than $\cdot CH_3$,[12] and with the consequent transfer of more electron density from cobalt(II) to $\cdot X$ (as in $Co^{III}-X^-$) than from cobalt(II) to $\cdot CH_3$ in the methyl-cobalt complexes. Further to this point, the 0.2 Å longer $Co-OH_2$ bond in $Co([14]aneN_4)(OH_2)CH_3^{2+}$[13,14] than in related acido-aquo-cobalt(III) complexes can be regarded as the manifestation of a relatively large amount of electron density in the d_{z^2} orbital, and the small homolysis