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TOTAL SYNTHESIS OF ANHYDRO LEVUGLANDIN D_2

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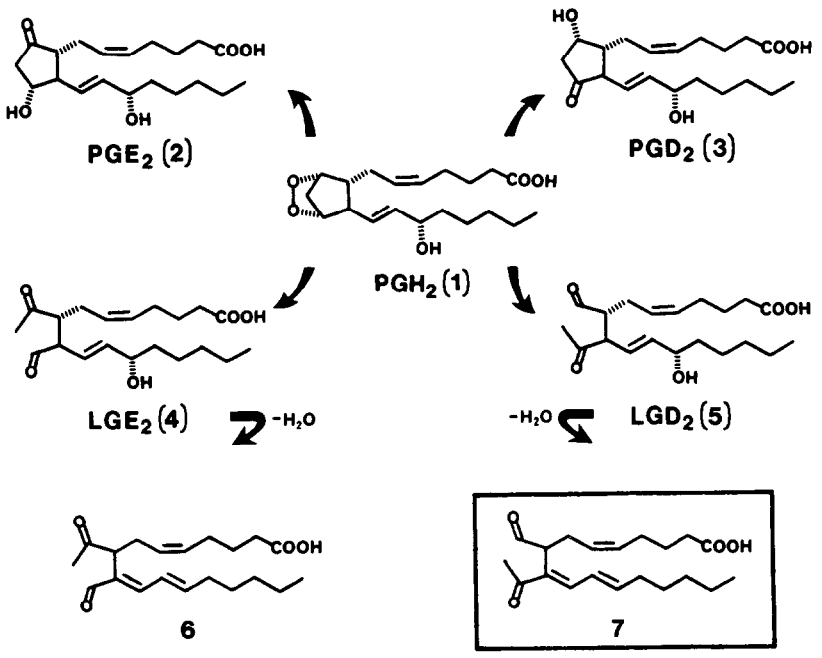
Abstract. Total synthesis of anhydro levuglandin D_2 [9-acetyl-8-formyl-5(Z),9(E),11(E)-heptadecatrienoic acid] confirms the structure assigned to this 9,10-seco prostanoic acid product from solvent induced rearrangement of the prostaglandin endoperoxide PGH_2 in aqueous solution.

The prostaglandin (PG) endoperoxide PGH_2 (1) is extraordinarily unstable in the aqueous environment of its biosynthesis.[1] Besides the prostaglandins PGE_2 (2) and PGD_2 (3) which were recognized previously as products of this decomposition,[1] two new aldehyde products were recently shown to be formed in about 20% combined yield.[2] Model studies[3] suggested that these new products are levulinaldehyde derivatives which we named levuglandin E_2 (LGE_2, 4) and levuglandin D_2 (LGD_2, 5) because of their respective relationship to E and D prostaglandins by aldol condensation (see scheme I).

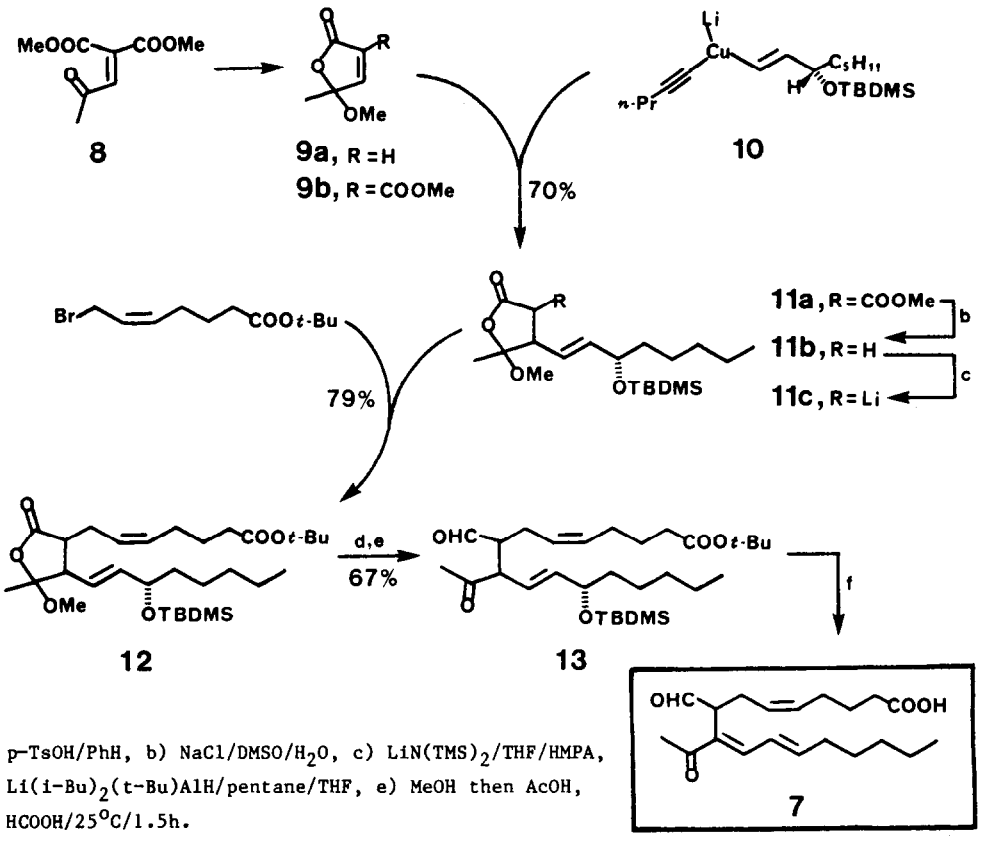
Scheme I



In contrast with thromboxanes which are 11,12-seco prostanoic acids, the E levuglandins are 10,11-seco and the D levuglandins are 9,10-seco prostanoic acids. Since the levuglandins are vinylogous β-hydroxy carbonyl compounds, they readily undergo dehydration affording anhydro derivatives 6 and 7. These dehydration products were both isolated recently.[4] However, ^1H NMR and mass

spectral data were deemed inadaquate for unambiguous distinction between 6 and 7. Therefore, total synthesis was desirable to firmly establish the identities of the E_2 and D_2 levuglandins. A short total synthesis of anhydro LGD_2 (7) is outlined in scheme II.

Scheme II



a) p-TsOH/PhH, b) NaCl/DMSO/H_2O, c) $LiN(TMS)_2$/THF/HMPA,
d) $Li(i\text{-}Bu)_2(t\text{-}Bu)AlH$/pentane/THF, e) MeOH then AcOH,
f) HCOOH/25°C/1.5h.

Our initial plan for construction of the intermediate 11b envisioned Michael addition of vinyl cuprate 10[5] to the α,β-unsaturated lactone 9a.[6] However, even in the presence of $MgBr_2$ (1 equiv) as a Lewis acid catalyst,[7] treatment of 9a with 10 in Et_2O-THF solution at -78° to 20°C followed by protic quench with 10% aqueous NH_4Cl led to recovery of 9a and formation of 3-t-butyldimethylsiloxyoct-1-ene. Therefore, the more electrophilic Michael acceptor 9b[8] was prepared by heating a benzene solution of dimethyl acetonylidenemalonate (8)[9] in the presence of p-toluenesulfonic acid (9 mol %). Treatment of 9b with vinyl cuprate 10 in ether solution at -78° to 20°C followed by protic quench with saturated aqueous NH_4Cl afforded 11a. Decarbomethoxylation of 11a was achieved by heating a solution in DMSO-water 5:1 (v/v) under reflux in the presence of NaCl (1 equiv).[10] The product lactone 11b was lithiated with lithium hexamethyldisilazane in THF at -78°C. Allylation of the lithium enolate 11c with t-butyl (Z)-7-bromohept-5-enoate[11] (1 equiv) in THF-HMPA 92:8 (v/v) at -40° to -20°C for 1h, followed by quenching with saturated aqueous NH_4Cl provided 12 which possesses the carbon skeleton of LGD_2. The t-butyl ester was chosen because of its expected

resistance to the aluminum hydride reduction[12] which is required for adjusting the oxidation level of 12. The key selective reduction was achieved in good yield using lithium di-i-butyl-t-butylhydridoaluminate in pentane-tetrahydrofuran at -78° to 20°C followed by quenching with methanol and then acetic acid. Note that the final product is the ketoaldehyde 13. The observed lack of overreduction suggests that the initially formed reduction product, a hemiacetal-mixed ketal, is not converted to 13 until the protic quench.

It is interesting that 13 appears to be less prone to dehydration than LGD_2 (5), the corresponding hydroxy acid. Thus, 13 is readily purified and isolated in 67% yield from the key reduction of 12. Treatment with formic acid does promote elimination and concomitant dealkylation of the ester to provide anhydro LGD_2 (7). The ^1H NMR and mass spectra of 7 are identical with those of anhydro LGD_2 obtained by solvent induced decomposition of PGH_2. These spectra are presented in figures 1 and 2. An E configuration for the 9,10 C=C bond is indicated by the ^1H NMR spectrum of 7

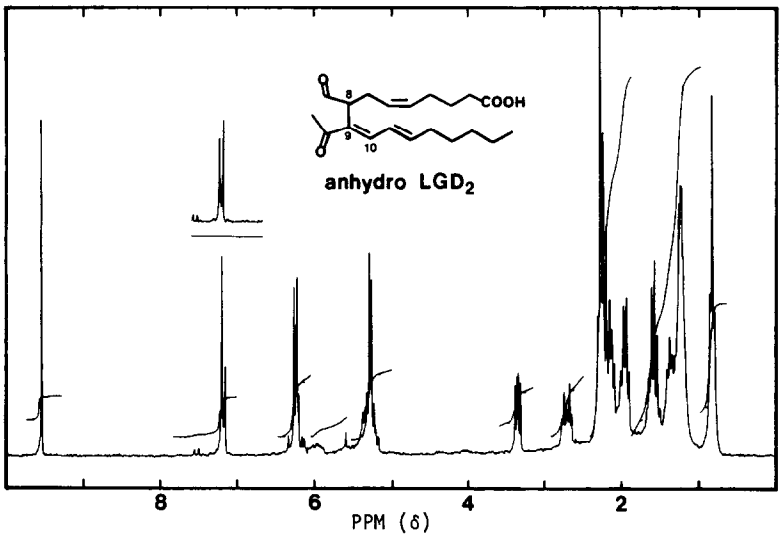


Figure 1. 200 MHz ^1H NMR spectrum of anhydro levuglandin D_2 in $CDCl_3$; inset shows C-10 hydrogen resonance of spectrum in CD_2Cl_2.

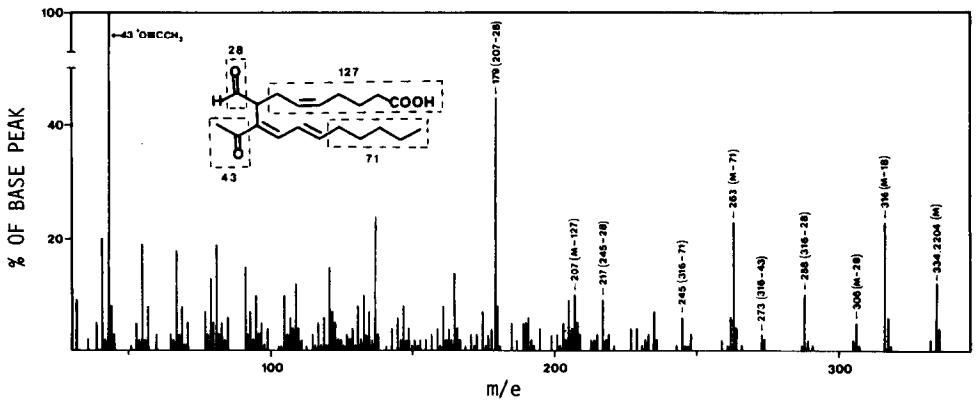


Figure 2. Mass spectrum of anhydro levuglandin D_2 (7).

since only one vinyl proton resonance appears at $\delta > 7.0$. The resonances for two vinyl protons, i.e. those on C_{10} and C_{11}, would be expected[13] to appear at $\delta > 7.0$ if the 9,10 C=C bond had the alternative Z configuration.

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References and Notes

1. (a) Hamberg, M.; Samuelsson, B. Proc. Nat. Acad. Sci. USA 1973, **70**, 899. (b) Hamberg, M.; Svensson, J.; Wakabayashi, T.; Samuelsson, B. ibid 1974, **71**, 345. (c) Nugteren, D.H.; Hazelhof, E. Biochim. Biophys. Acta 1973, **326**, 448. (d) Raz, A.; Kenig-Wakshal, R.; Schwartzman, M. ibid 1977, **488**, 322. (e) Nugteren, D.H.; Christ-Hazelhof, E. Adv. Prostaglandin Thromboxane Res. 1980, **6**,129.
2. (a) Zagorski, M.G.; Salomon, R.G. J. Am. Chem. Soc. 1982, **104**, 3498. (b) Salomon, R.G.; Miller, D.B.; Zagorski, M.G.; Coughlin, D.J. ibid 1984, in press.
3. (a) Salomon, R.G.; Salomon, M.F.; Coughlin, D.J. ibid 1978, **100**, 660. (b) Salomon, R.G.; Coughlin, D.J. ibid 1979, **101**, 2761.
4. Miller, D.B.; Lal, K.; Salomon, R.G. ibid 1984, submitted.
5. Corey, E.J.; Beames, D.J. ibid 1972, **94**, 7210.
6. Seltzer, S.; Stevens, K.D. J. Org. Chem. 1968, **33**, 2708.
7. (a) Salomon, R.G.; Miller, D.B.; Raychaudhuri, S.R.; Avasthi, K.; Lal, K. J. Am. Chem. Soc. 1984, submitted. (d) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. J. Org. Chem. 1982, **47** 119.
8. 9b shows m.p. 68-70°C, white flakes from Et_2O; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.70(s,3H), 3.27(s,3H), 3.8(s,3H), 7.84(s,H).
9. (a) Ouali, M.S.; Vaultier, M.; Corrie, R. Synthesis 1977, 626. (b) Mayring, L.; Severin, T. Chem. Ber. 1981, **114**, 3863.
10. Krapcho, A.P.; Lovey, A.J. Tetrahedron Lett. 1973, 957.
11. This bromoester was prepared from 7-tetrahydropyranyloxy-5-heptynoic acid [(a) Martel, J.; Toromanoff, E. German Patent **2,121,361** (1971); Chem. Abstr. 1972, **76**, 24712d. (b) Corey, E.J.; Sachdev, H.S. J. Am. Chem. Soc. 1972, **95**, 8483. (c) Martel, J.; Blade-Font, A.; Marie, C.; Vivat, M.; Toromanoff, E.; Buendia, J. Bull. Soc. Chim. Fr. II 1978, 131] by t-butylation with N,N-dimethylformamide di-t-butylacetal [Widmer, V. Synthesis 1983, 135], selective hydrolysis of the tetrahydropyranyl acetal with acetic acid in THF [Bernady, K.F.; Floyd, M.B.; Poletto, J.F.; Weiss, M.J. J. Org. Chem. 1979, **44**, 1438], partial hydrogenation in the presence of palladium on barium sulfate and synthetic quinoline [Cram,D.J.; Allinger, N.L. J. Am. Chem. Soc. 1955, **78**, 2518] and treatment of the resulting alcohol with PBr_3 in ether solution at 0°-35°C.
12. Greene, T.W. "Protective Groups in Organic Synthesis", John Wiley & Sons, New York, p. 317 (1981).
13. Ananthasubramanian, L.; Carey, S.T.; Nair, M.S.R. Tetrahedron Lett. 1978, 3527, and references cited therein.

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