coenzyme Q_1 without comments on the formation of regioisomers, using 4 equiv of π-allylnickel complex to 1 equiv of the quinone (see ref 4b).

(8) In other allylations of quinones polyalkylation, chromanol formation, side-chain cyclization, and other numerous difficulties concerned with product isolations are often observed: D. E. Wolf, C. H. Hoffman, N. R. Trenner, B. H. Arison, C. H. Shunk, B. O. Lin, J. F. McPherson, and K. Folkers, *J. Am. Chem. Soc.*, **80**, 4752 (1958); U. Gloor, O. Isler, R. A. Morton, R. Rüegg, and O. Wiss, *Helv. Chim. Acta*, **41**, 2357 (1958).

(9) Under the similar conditions to that of quinones, the α,β-unsaturated ketone gave the usual 1,4-conjugate addition product with allyltin.

(10) In addition, using BF_3·OEt_2 as activator of carbonyl, our reaction proceeds under mild conditions in contrast to the usual insertion reaction of the carbonyl group (ketone or aldehyde) into the allyltin Sn–C bond. Without BF_3·OEt_2 the usual reaction is limited to polarized carbonyls attached to electron-withdrawing groups or needed higher reaction temperature: (a) K. König and W. P. Neumann, *Tetrahedron Lett.*, 495 (1967); (b) C. Servans and M. Pereyre, *J. Organomet. Chem.*, **26**, C4 (1971); (c) *Ibid.*, **35**, C20 (1972); (d) E. A. Abel and R. J. Rowley, *Ibid.*, **84**, 199 (1975).

(11) Allylations using other allylating reagents such as allylsilane[4d] and π-allylnickel complex[4b,c] have been reported [see also Hegedus et al., *J. Am. Chem. Soc.*, **100**, 3461 (1978)]. However, coenzyme Q_1 was first prepared in a satisfactory yield by our procedure.

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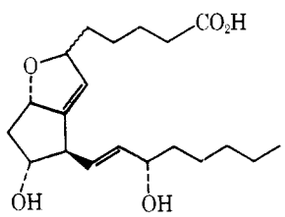
Synthesis of (6*R*)- and (6*S*)-6(9)-Oxy-11,15-dihydroxyprosta-7,13-dienoic Acids [(6*R*)- and (6*S*)-Δ⁷-PGI₁]: Nonidentity with the Proposed Arachidonic Acid Metabolite

Summary: This report describes the chemical synthesis of (6*R*)- and (6S)-Δ⁷-PGI_1; the spectral properties of the synthetic material were entirely different from those reported by Pace-Asciak and Wolfe for their proposed biosynthetic arachidonic acid metabolite.

Sir: In 1971, Pace-Asciak and Wolfe[1] reported the formation of two novel prostanoic acid derivatives during the incubation of arachidonic acid with rat stomach homogenates. The structure of the major component was assigned as 6(9)-oxy-11,15-dihydroxyprosta-7,13-dienoic acid (**1**) and the minor component as 6(9)-oxy-11,15-dihydroxyprosta-5,13-dienoic acid (**2**). The structural assignments of **1** and **2**[2] were based



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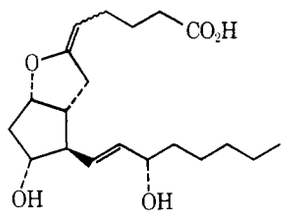
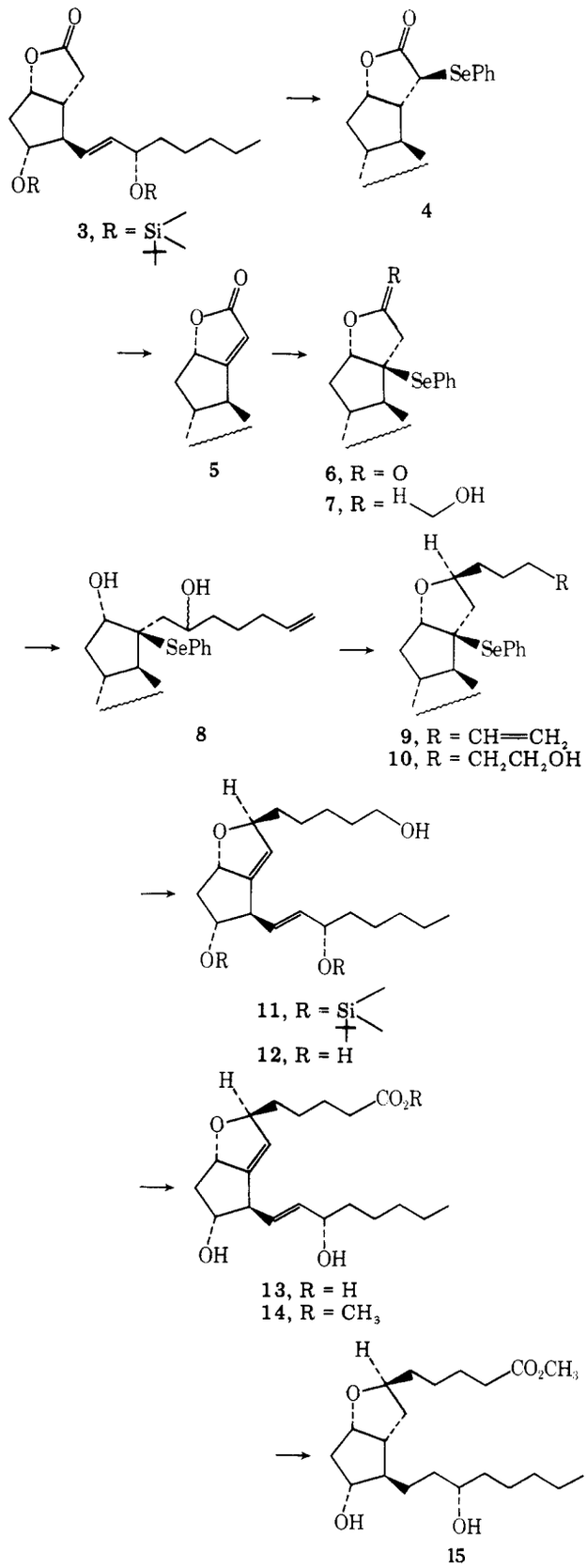


2

on mass spectrometric evidence and products derived from oxidative ozonolysis. The recent discovery[3] of prostacyclin (PGI_2), the 5*Z* isomer of **2**,[4-6] has revived interest in this area of prostaglandin research.[7-9] In view of the finding that PGI_2 is rapidly hydrolyzed to 6-oxoprostaglandin $F_1\alpha$ at pH's as high as 7.6,[4] the isolation of **2** under the acidic conditions employed[1] must be regarded as unlikely. However, the existence of a structurally related 6(9)-oxy-11,15-dihydroxyprosta-7,13-dienoic acid (**1**, Δ⁷-PGI_1) cannot be excluded on this basis. In this communication we describe a chemical synthesis of (6*R*)- and (6*S*)-Δ⁷-PGI_1 and compare the nuclear magnetic resonance and mass spectrometric properties of our synthetic material to those reported by Pace-Asciak and Wolfe for their alleged biosynthetic metabolite.

Reaction of the 11,15-bis(dimethyl-*tert*-butylsilyl) lactone **3** in tetrahydrofuran (THF) with 1.1 equiv of lithium diisopropylamide (−78 °C, 15 min) and treatment of the resulting enolate with 1.3 equiv of PhSeCl for 20 min at −78 °C afforded the 7-phenylselenenyl lactone **4** in 90% yield (Scheme I).[10] Exposure of lactone **4** in CH_2Cl_2 to 10% aqueous H_2O_2 (10 equiv, room temperature for 1 h) gave via phenyl selenoxide elimination the α,β-unsaturated lactone **5** [mp 36.5–38 °C; UV

Scheme I



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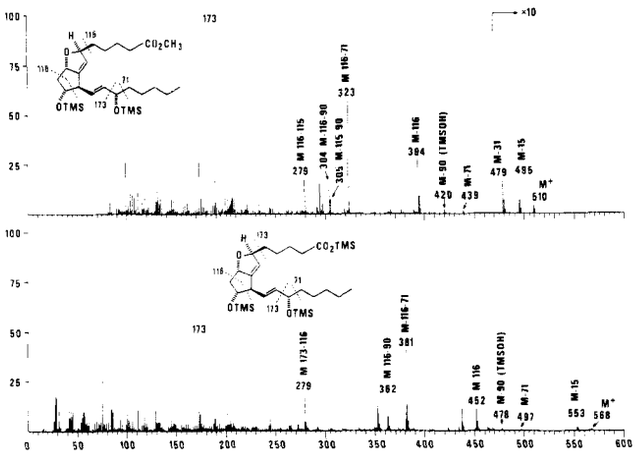
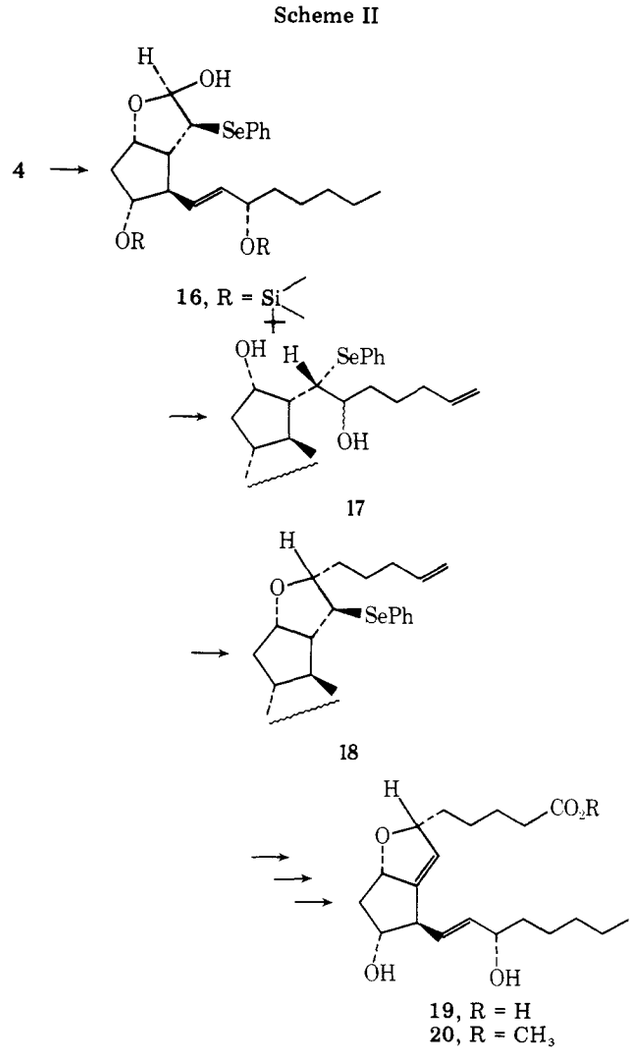


Figure 1. Mass spectra of synthetic **14** (trimethylsilyl ether methyl ester derivative) and **13** (trimethylsilyl ether trimethylsilyl ester derivative).

(EtOH) 217 nm (ε 13 950)]. Addition of lactone **5** in EtOH to a solution of phenylselenenyl anion (generated in situ from 1.2 equiv of PhSeSePh and $NaBH_4$ in EtOH) yielded the 8-phenylselenenyl lactone **6** (R_f values observed on silica gel TLC plates with ethyl acetate–benzene, 50:1, as solvent: 0.49 for **4** and 0.42 for **6**). The lactol **7** was obtained by reduction of lactone **6** in toluene with diisobutylaluminum hydride (1.2 equiv, −78 °C for 20 min). Alkylation of lactol **7** in ether with 4-pentenylmagnesium bromide (3–4 equiv, 0–5 °C for 1.5 h) afforded the 6,9-dihydroxy olefin **8** (63% yield overall from **4**). The formation of the 6,9-epoxy linkage from diol **8** was achieved either with 5 equiv of *p*-toluenesulfonyl chloride in pyridine at 40 °C for 48 h, or with 2 equiv of methanesulfonyl chloride and 5 equiv of Et_3N in CH_2Cl_2 at −78 °C for 5 min. In each instance, the (6*S*)-6,9-epoxy isomer **9** was obtained as the exclusive 6,9-cyclized product.[11] The stereochemical assignment of **9** was made from the experiments later discussed. Conversion of **9** to (6*S*)-Δ^7-PGI_1 (**13**) was accomplished (50% overall yield) by the sequence: (a) hydroboration of **9** with 9-borobicyclo[3.1.1]nonane[12] followed by careful oxidative workup furnished the C-1 primary alcohol **10;** (b) oxidative treatment of **10** with 10% aqueous H_2O_2 yielded the unsaturated bis(silyl) ether **11;** (c) mild acid hydrolysis of **11** gave the 11,15-dihydroxy C-1 alcohol **12;** and (d) selective oxidation of **12** with Pt and O_2[13] afforded (6*S*)-Δ^7-prosta-7,13-dienoic acid **13** (R_f value 0.28, 2% acetic acid in ethyl acetate as solvent). Catalytic hydrogenation (5% Pd–C) of (6*S*)-Δ^7-PGI_1 methyl ester **14** (R_f value, 30% acetone in methylene chloride as solvent, 0.28 for **14;** R_f 0.33 for PGI_2 methyl ester) gave a single product. This material was identical by TLC, ^1H NMR, and MS with an authentic sample of (6*S*)-13,14-dihydro-PGI_1 methyl ester[14] (**15**), but different from (6*R*)-13,14-dihydro-PGI_1 methyl ester.[14]

The spectral data for **13** and **14** are consistent with their assigned structures. However, the ^1H NMR and MS spectral properties of synthetic **13** and **14** are clearly not in agreement with those published by Pace-Asciak and Wolfe for the biosynthetic metabolite **1.** High or low resolution mass spectra of **13** and **14** gave the correct molecular ion (Figure 1).[15] A characteristic pattern of mass fragmentation of **13** and **14** shows the preferential elimination of $CH_2{=}CHOSiMe_3$ ($M^+ - 116$), while in the spectra of the biosynthetic derivatives it is distinctly absent. Conversely, the base peak (*m/e* 225) present in Pace-Asciak and Wolfe's spectra is totally absent in **13** and **14.** The ^1H NMR ($CDCl_3$) spectrum of methyl ester **14** shows a three-hydrogen multiplet in the olefinic region (δ 5.60), a signal at δ 3.00 (C-12 hydrogen) characteristic for all

Scheme II



the Δ^7-intermediates prepared in this study, and a multiplet centered at δ 5.00 (C-6 and C-9 hydrogens). The latter absorption is unmistakably absent in the biosynthetic sample. The ^{13}C NMR of **14** reveals four unsaturated carbons. As expected, the chemical shifts (Me_4Si reference) of carbons C_{13} (130.0 ppm) and C_{14} (133.8 ppm) corresponded to those of the C_{13} and C_{14} carbons of (6*S*)-PGI_1 methyl ester. An off-resonance decoupling study allowed positive assignment of the chemical shifts at 146.8 and 122.7 ppm to the C_8 quaternary carbon and C_7 tertiary carbon, respectively.

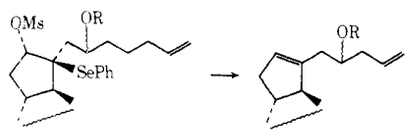
To unequivocally rule out the possibility that a difference in stereochemistry at C-6 was responsible for the variation in spectral properties, we sought a synthesis of (6*R*)-Δ^7-PGI_1. Following the reaction conditions previously described, reduction of lactone **4** gave lactol **16** (90%), which after Grignard alkylation, furnished the 7-phenylselenenyl diol **17** in 45% yield[16] (Scheme II).[10] Treatment of the diol **17** in CH_2Cl_2 with *N,N*-diethyl-*N*-methylmethanesulfonylammonium fluorosulfonate[17] (1.5 equiv, 0–5 °C) in a catalytic amount of pyridine yielded only the (6*R*)-epoxy isomer **18.**[18] Having achieved the synthesis of **18,** the remaining steps leading to (6*R*)-Δ^7-PGI_1 (**19**) were accomplished in the same manner[19] as discussed for the synthesis of (6*S*)-Δ^7-PGI_1 (**13**) from **9.** The (6*R*)-Δ^7-PGI_1 isomer (**19**) and its methyl ester derivative **20,** as well as the (6*R*)-Δ^7 intermediates, all appeared slightly less polar on TLC than the corresponding (6*S*)-Δ^7 compounds (R_f values, 2% acetic acid in ethyl acetate, 0.33 for **19**; 30% acetone in methylene chloride, 0.33 for **20**). With the exception of minor differences in ion intensities, the mass spectra of **19** and **20** are identical with those of the (6*S*)-Δ^7 isomers **13** and **14.**

The ^{1}H NMR spectra of **19** and **20** were very similar but not identical with those of **13** and **14**. As expected, the most noticeable differences appeared in the olefin absorption region.

From the data described above we must conclude that the structure proposed by Pace-Asciak and Wolfe for their biosynthetic metabolite is incorrect. Further aspects of this research regarding the origin of this unknown arachidonic acid metabolite are under investigation in our laboratory.

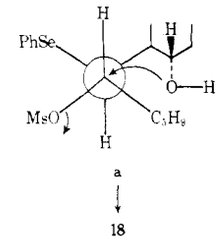
References and Notes

(1) C. Pace-Asciak and L. S. Wolfe, *Biochemistry*, **10**, 3657 (1971).
(2) These investigators[1] isolated **1** and **2** as an unseparable mixture termed fraction A; the mass spectral data were obtained with fraction A.
(3) S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature (London)*, **263**, 663 (1976); S. Moncada, E. A. Higgs, and J. R. Vane, *Lancet*, **1**, 18 (1977); G. J. Dusting, S. Moncada, and J. R. Vane, *Prostaglandins*, **13**, 3 (1977), and references contained therein.
(4) R. A. Johnson, D. R. Morton, J. H. Kinner, R. A. Gorman, J. C. McGuire, F. Sun, N. Whittaker, S. Bunting, J. Salmon, S. Moncada, and J. R. Vane, *Prostaglandins*, **12**, 915 (1976).
(5) E. J. Corey, G. E. Keck, and I. Szekely, *J. Am. Chem. Soc.*, **99**, 2006 (1977).
(6) R. A. Johnson, F. H. Lincoln, J. L. Thompson, E. G. Nidy, S. A. Mizsak, and U. Axen, *J. Am. Chem. Soc.*, **99**, 4182 (1977).
(7) J. Fried and J. Barton, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 2199 (1977).
(8) K. C. Nicolaou, W. E. Barnette, G. P. Gasic, and R. L. Magolda, *J. Am. Chem. Soc.*, **99**, 7736 (1977).
(9) C. J. Sih and Fu-Chih Huang, *J. Am. Chem. Soc.*, **100**, 643 (1978).
(10) All new compounds gave spectral data consistent with the assigned structures as well as satisfactory analytical figures via combustion analysis or high-resolution spectrometry. Complete spectral data are available upon request.
(11) With either reagent we obtained a 45–50% isolation yield of **9**. The remaining material (30–35%) consisted of Δ^8-olefins resulting from mesylation at C-9 followed by elimination. The rationale for the stereoselective outcome of this cyclization is under investigation.
(12) R. Liotta and H. C. Brown, *J. Org. Chem.*, **42**, 2836 (1977).
(13) J. Fried and J. C. Sih, *Tetrahedron Lett.*, 3899 (1973).
(14) The authors thank Dr. N. A. Nelson and Dr. R. A. Johnson for supplying authentic samples of (6*R*)- and (6*S*)-13,14-dihydro-PGI$_1$ methyl esters. For assignment of stereoconfiguration of 5,6-dihydroprostacyclins (PGI$_1$'s) see N. A. Nelson, *J. Am. Chem. Soc.*, **99**, 7362 (1977).
(15) The low resolution spectra of **13** and **14** were recorded on the same derivatives and under the identical conditions as reported by Pace-Asciak and Wolfe in ref 1.
(16) Grignard addition to lactol **16**, in contrast to lactol **7**, was seriously hampered by reductive cleavage of the 7-phenylselenenyl group which gave after isolation the unsubstituted lactol in equal amount.



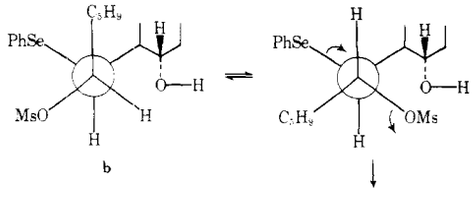
R = H, OSO_2CH_3

(17) J. F. King and J. R. duManoir, *J. Am. Chem. Soc.*, **97**, 2566 (1975).
(18) Use of mesyl chloride–Et_3N produced **18** in poorer yield (27%) and increased amounts of Δ^6-olefin derived products. The formation of a single (6*R*)-6,9-cyclized isomer (**18**) can be rationalized if one considers the preferred conformers available for an internal S_N2 displacement of the (6*R*)- and (6*S*)-mesylate isomers. The preferred conformer a leading to the formation of **18** would place the phenylselenenyl and pentenyl groups in a favored, sterically less crowded anti relationship. In contrast the required (6*R*)-mesylate conformer b forces the pentenyl group into a less favored gauche relationship with the phenylselenenyl group. In this instance 6,9-ether formation is diverted and elimination to olefin is the major pathway. However, as in the case of **8** one cannot exclude the possibility that Grignard addition to lactols **7** and **16** proceeded in a stereoselective manner to generate a single C-6 isomer.



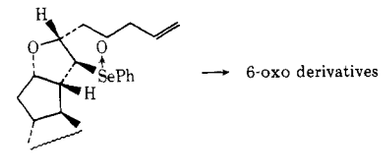
a

18



Δ^6-olefin derivatives

(19) Under the same conditions which affected selenoxide elimination from **4** and **10**, one is able to isolate selenoxide a. The desired Δ^7-olefin was obtained in 30% yield after warming a in CH_2Cl_2 at 45 °C. The low yield



a

can be attributed in part to the nonselective elimination of selenoxide a. After aqueous workup and chromatography, we inevitably always isolated some 6-oxo derived products.

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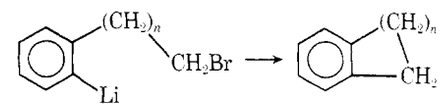
A New Anionic Cyclization of the Parham Type. Selective Ring Opening of Epoxides

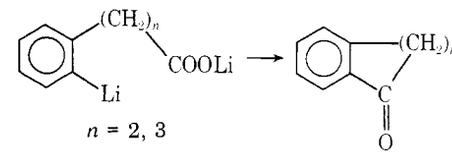
Summary: Epoxides derived from *o*-bromophenyl allyl ethers undergo bromine–lithium exchange with butyllithium at −100 °C. The resulting lithium reagents undergo cyclization by exo attack on the epoxide linkage as predicted by the Baldwin rules.

Sir: Of the synthetic possibilities opened up by Parham's development of functionalized aryllithium reagents,[1] the most important involve novel cyclization reactions which can be effected when the functional group is ortho to the lithium atom. While the majority of these ring closures involved the addition of an external electrophile, examples were provided of two novel reactions in which the electrophile is in the side chain, but remains passive until the halogen–metal exchange on the aryl nucleus is complete. These two reactions, the Parham cyclialkylation[2] (eq 1) and cycliacylation[3,4] (eq 2), have both found immediate application to important synthetic problems.[5-7]



(1)

n = 1, 2



(2)

n = 2, 3

It seemed likely that there should be other electrophilic groups which at −100 °C would remain passive long enough to permit halogen–metal exchange to occur. Of these the epoxide linkage appeared particularly interesting, for in theory rings of two different sizes might be produced. Reaction of monosubstituted epoxides with Grignard[8] and organolithium[9] reagents has been demonstrated to take place with anionic attack preferentially at the unsubstituted end. On the other

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