or warming to room temperature. Although the reactivity of **3**, compared to **2**, precludes further purification at present, the pmr signals are evidently due to **3** and the maleic anhydride adduct (**12**) of **3** has been well characterized (see Table I). Using the C-2 proton (δ 6.42) of cyclopentadiene as a reference, the difference, $\Delta\delta = 1.04 = 6.42 - 5.38$, may be taken as the paramagnetic contribution by the induced ring current in **3**. If one neglects the perturbation of the electronic structure of **1** caused by the three *tert*-butyl substituents of **3** and then adopts (i) the equation (1)[18] to calculate the induced ring current in an [M]annulene, advanced by Pople and Untch,[18] (ii) the rectangular geometry predicted by Dewar,[19] and (iii) Coulson and Golebiewski's equation for the estimate of λ,[20] one obtains a paramagnetic contribution of 1.18 ppm for [4]annulene. The agreement between the experimental and calculated values is excellent, but subject, of course, to the arbitrary choice of the reference compound.[21]

We conclude this note with a remark concerning the ground-state multiplicity of **1**. In repeated experiments, the esr spectra of **1** generated in a manner previously reported[3,22] showed no indication of signals that can be attributed to the triplet ground state of **1**, as in the case of tetramethyl[4]annulene.[4] These results, the observation of sharp nmr signals of **2** and **3** and the above adoptation of Dewar's theoretical treatment, all are, at least superficially, incompatible with the conclusion about the geometry of **1** drawn from its infrared spectra[2,5] and implications of their theoretical treatment.[2] These subtle, important points remain to be clarified.[23]

(18) J. A. Pople and K. G. Untch, *J. Amer. Chem. Soc.*, **88**, 4811 (1966). The equation (1) is

$$I = -(\pi^2 e^2 \beta_0 / h^2 c) S(32\lambda^{1/2} M^2) \times \sum_{j}^{occ} [1 + 2\lambda \cos(4\pi j/M) + \lambda^2]^{-3/2} [\lambda + (1 + \lambda^2) \times \cos(4\pi j/M) + \lambda \cos^2(4\pi j/M)]$$

where I, S, λ, and β_0 are induced ring current per unit magnetic field, area of the ring, the degree of band alternation, and β value for benzene, respectively. $\Delta\delta = Ix$ spatial factor (Biot-Savart law).

(19) M. J. S. Dewar, M. C. Kohn, and N. Trinajstic, *J. Amer. Chem. Soc.*, **93**, 3437 (1971).

(20) C. A. Coulson, and A. Golebiewski, *Proc. Phy. Soc., London*, **78**, 1310 (1961).

(21) A referee has suggested that cyclobutene (C-1 H, δ 5.97) would be a better reference. We have chosen cyclopentadiene as a cyclic diene closest in structure to [4]annulene without a significant ring current, if any. In either case the calculated value is consistent with experiment.

(22) The possible detention of **1** in methyltetrahydrofuran at 77°K is owing to the rigidity of its matrix compared to that of an inert gas. *Cf.* ref 2 and 5. Our precursor (**13**) of **1** is now relatively readily available from the 2:1 adduct of [4]annuleneiron tricarbonyl and acetylenedicarboxylate, as found by H. Prinzbach, *et al.*, private communication, June 13, 1973.

(23) We are grateful to Mr. K. Morio of this laboratory for the calculation of $\Delta\delta$ and to the National Research Council of Canada for financial support.

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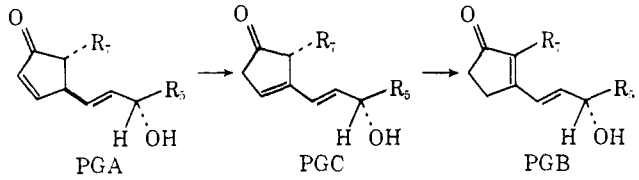
A Simple Synthesis of 8-Methylprostaglandin C_2

Sir:

One pathway for deactivation of prostaglandin A_2 (PGA_2) in mammalian blood is the conversion *via* PGC_2[1] to PGB_2. In view of this possibility and also the recently discovered biological potency of PGC_2,[1] we have undertaken the development of a synthesis of 8-MePGC_2, a substance which is structurally protected against transformation to the PGB_2 series. An especially simple synthetic route to 8-MePGC_2 (**9**) is reported here.



2-Methylcyclopentane-1,3-dione, a common and readily available intermediate for steroid total synthesis,[2] was converted by reaction with thallous ethoxide (1 equiv) in tetrahydrofuran (THF) into the colorless thallium salt (recrystallized from ethanol), which upon heating with methyl 7-iodo-5-heptynoate[3] (1 equiv) in a few volumes of benzene at 62–64° for 5–6 days afforded the C-alkylation product **1**[4] in 87% yield as a colorless oil.[5] Reduction of **1** using Lindlar's catalyst-hydrogen afforded quantitatively the *cis* olefin **2** (colorless oil). Reaction of **2** with an ethereal solution of the lithium reagent **3**,[6] prepared from (*S*)-3-*tert*-butyldimethylsilyloxy-*trans*-1-octenyl iodide in ether and 2 equiv of *tert*-butyllithium (in hexane),[6] afforded the desired tertiary alcohol, **4** (mixture of stereoisomers), in addition to some unchanged **2**. Treatment of the mixture with thionyl chloride (3 equiv) and pyridine (7 equiv) in methylene chloride at −30 to −35° for 12 hr, followed by chromatography to separate **2** from the dehydration product, gave the two diastereomeric 8-MePGC_2 derivatives **5** and **6** (30% overall yield from **2**,[7] uv_{max}

(1) (a) R. L. Jones, *J. Lipid Res.*, **13**, 511 (1972); (b) R. L. Jones and S. Cammock, *Advan. Biol. Sci.*, **9**, 61 (1973).

(2) We are indebted to Dr. Horst Witzel of Schering AG, Berlin, and Dr. Herchel Smith, Wyeth Laboratories, Philadelphia, Pa., for generous gifts of this intermediate which is also commercially available.

(3) This iodide was prepared by the following sequence. Propargyl tetrahydropyranyl ether → lithium derivative (1 equiv *n*-BuLi in THF) → 6-chloro-2-octyn-1-ol tetrahydropyranyl ether (1-chloro-3-bromopropane in THF, 20 hr at 70–75°) (80% yield) [see A. I. Rachlin, N. Wasyliw, and M. W. Goldberg, *J. Org. Chem.*, **26**, 2688 (1961)] → 6-cyano-2-octyn-1-ol tetrahydropyranyl ether (sodium cyanide in dimethyl sulfoxide at 40–45° for 48 hr and 55° for 3 hr) (95% yield) → 7-tetrahydropyranyloxy-5-heptynoic acid (10% sodium hydroxide in aqueous methanol at reflux for 16 hr) (95% yield) → methyl 7-tetrahydropyranyloxy-5-heptynoate (CH_2N_2 in ether) (97% yield) → methyl 7-hydroxy-5-heptynoate (Amberlite IR 120, acid form, methanol 3 hr at 25°) (97% yield) → methyl 7-bromo-5-heptynoate (triphenylphosphite–bromine complex–pyridine in THF at 0° for 1 hr and 20° for 3 hr) (90% yield) [see D. K. Black, S. R. Landor, A. N. Pate], and P. F. Whiter, *Tetrahderon Lett.*, 483 (1963)] → methyl 7-iodo-5-heptynoate (excess sodium iodide in acetone at 25° for 20 hr) (99% yield). A similar process has been used by Bagli, *et al.*, for the preparation of this iodo ester [personal communication from J. F. Bagli and also J. F. Bagli and T. Bogri, *Tetrahedron Lett.*, 3815 (1972)].

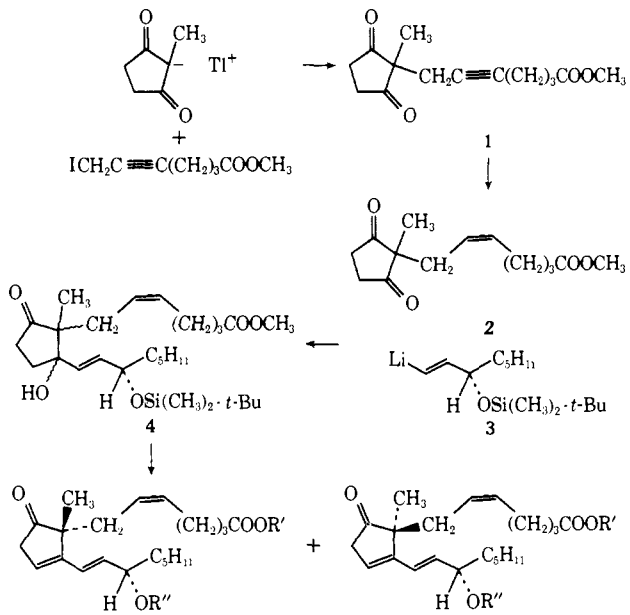
(4) The structures assigned to the substances reported herein are supported by infrared and proton magnetic resonance spectra and molecular formula determination by high-resolution mass spectra using an AEI MS-9 instrument. Samples employed for spectral characterization were homogeneous by chromatographic analysis (tlc or high-pressure liquid chromatography) using several solvent systems.

(5) For the use of thallium salts in the C-alkylation of β-dicarbonyl compounds, see E. C. Taylor, G. H. Hawks, III, and A. McKillop, *J. Amer. Chem. Soc.*, **90**, 2421 (1968).

(6) (a) E. J. Corey and D. J. Beames, *J. Amer. Chem. Soc.*, **94**, 7210 (1972); (b) E. J. Corey and J. Mann, *ibid.*, **95**, 6832 (1973).

(7) The mixture of diastereomeric ester silyl ethers **5** and **6** could not be separated chromatographically and, for example, showed only a single spot of R_f 0.73 after tlc on silica gel using methyl chloride–ethyl acetate (15:1) for development.

235 nm (ε 19,200) (in CH_3OH), ir_{max} 1734 cm^{-1} (in $CHCl_3$). Hydrolysis of the mixture of **5** and **6** using acetic acid–THF–water (3:1:1) at 22–23° for 20 hr produced the corresponding hydroxy esters **7** and **8** which could be separated by careful thin-layer chromatography on silica gel using two developments with methylene chloride–ethyl acetate (20:1). The isomers of higher R_f (0.31) and lower R_f (0.25) are provisionally assigned structures **7** and **8**, respectively, on the basis of biological activities (see below).[8] The more polar isomer, obtained as a colorless air-sensitive oil, had $[\alpha]^{25}D$ +10.32° (*c*, 1.74 in $CHCl_3$) and showed uv_{max} at 235 nm (ε 19,000) (in CH_3OH) and ir_{max} at 1742 cm^{-1} with a shoulder at 1733 cm^{-1} (in CH_2Cl_2), whereas the less polar isomer was somewhat less dextrorotatory, $[\alpha]^{25}D$ +2.8° (*c*, 1.36 in $CHCl_3$), and showed the same ultraviolet and infrared carbonyl absorption. The methyl esters **7** and **8** were converted in high yield to the corresponding free acids **9**, $[\alpha]^{25}D$ +2.45° (*c*, 1.3 in $CHCl_3$), and **10**, $[\alpha]^{25}D$ +13.6° (*c*, 1.1 in $CHCl_3$), by the action



5, R' = CH_3; R" = $Si(CH_3)_2$·*t*-Bu
6, R' = CH_3; R" = $Si(CH_3)_2$·*t*-Bu
7, R' = CH_3; R" = H
8, R' = CH_3; R" = H
9, R' = R" = H
10, R' = R" = H

of porcine pancreatic lipase[9] at pH 7.5 and 25° in water containing a small amount of dimethylformamide. Both **9** and **10** showed infrared carbonyl absorption at 1742 and 1710 cm^{-1} (in CH_2Cl_2) and ultraviolet absorption at 234 nm (ε 14,500) (in CH_3OH). In the solvent system benzene–dioxane–acetic acid (90:10:1) on a silica gel thin layer, samples of **9**, **10**, and PGA_2 showed R_f values of 0.175, 0.216, and 0.145, respectively. The biological activity of **9** was 10–30 times greater than that of **10** in tests of stimulation of contraction of smooth muscle (guinea pig uterus), suggesting the tentative configurational assignments indicated herein.[10]

The simple and effective synthesis of 8-MePGC_2 (**9**) described above makes available a biologically active member of the PGC_2 family which in contrast to the highly sensitive PGC_2 cannot undergo deactivation *via* a PGB structure.[11,12]

(8) The diastereomers (former in *ca.* 1:1 ratio) were cleanly separated by high-pressure liquid chromatography using a Waters Associates ALC-202 instrument fitted with a Porasil T column. Retention times using an 8 ft × 0.125 in column, 5% ether in methylene chloride as solvent and a flow rate of 1.2 ml/min were 83 min and 60 min for 7 and **8**, respectively.

(9) Obtained as a gift from Dr. H.-J. Hess of the Chas. Pfizer Co.

(10) We are indebted to Dr. H.-J. Hess and associates of the Chas. Pfizer Co. Medical Research Laboratories for the biological tests. The isomer designated as **9** was one-thirtieth as active as PGE_2 in the smooth muscle test. Both esters 7 and **8** were found to be active in inhibition of gastric acid secretion in rats (*ca.* 60% of PGE_2 or PGA_2).

(11) For a synthetic route to PGC_2 itself, see, E. J. Corey and G. Moinet, *J. Amer. Chem. Soc.*, **95**, 7185 (1973).

(12) This work was assisted financially by the National Institutes of Health and the Chas. Pfizer Co.

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Retention in the Combination of Optically Active 2-Butyl-*tert*-Butoxy Radical Pairs

Sir:

We wish to report the results of our investigation of the optical purity of *S*-(+)-2-butyl *tert*-butyl ether obtained from thermolysis of *S*-(+)-*tert*-butylperoxy 2-methylbutyrate at 101.8° in solvents of varying fluidity. The results allow an estimation of the ratios of the rate constants for internal rotation (k_r) and tumbling (k_t) to that for combination of the 2-butyl-*tert*-butoxy radical pair. The k_t/k_c ratio was found to be *ca.* ten times that reported[1] for benzylic radical pairs. The fluidity dependence of the ratio is *ca.* 100 times that estimated from data recently reported for a fluorenyl–diazenyl pair.[2]

The specific optical rotation of the ether was obtained by relating it to *S*-(+)-2-butanol. Sodium pivalate was oxidatively decarboxylated in an electrolysis cell containing 0.02 *M* *S*-(+)-2-butanol ($[\alpha]^{23}°_{589}$ +9.31 ± 0.08° (*c*, 2.60, CCl_4), 67.1% optically pure[3]) dimethylformamide solution. The resulting 2-butyl *tert*-butyl ether showed a specific rotation of +6.17 ± 0.06° (*c*, 2.76, CCl_4; 23°, 589 nm). A sample of this material was cleaved by trifluoroacetic acid and the resulting *S*-(+)-2-butanol ($[\alpha]^{23}°_{589}$ +9.27 ± 0.08° (*c*, 3.38, CCl_4), 66.9% optically pure) was essentially unchanged in optical purity relative to unreacted alcohol recovered from the electrolysis ($[\alpha]^{23}°_{589}$ +9.35 ± 0.05° (*c*, 6.41, CCl_4), 67.4% optically pure). The specific rotation of optically pure *S*-(+)-2-butyl-*tert*-butyl ether ($[\alpha]^{23}°_{589}$ +9.19 ± 0.10°) was thus calculated from the known optical purity of the *S*-(+)-2-butanol used in this sequence.

The *S*-(+)-2-butanol was obtained from *S*-(+)-2-methylbutanoic acid through a carboxy inversion–hydrolysis sequence[4] *via* the mixed peroxide with *m*-

(1) (a) K. R. Kopecky and T. Gillian, *Can. J. Chem.*, 47, 2371 (1969); (b) F. D. Greene, M. A. Berwick, and J. C. Stowell, *J. Amer. Chem. Soc.*, **92**, 867 (1970).

(2) R. A. Johnson and S. Seltzer, *J. Amer. Chem. Soc.*, **95**, 938 (1973).

(3) (a) All optical rotation samples were purified by glpc. (b) P. J. Leroux and H. J. Lucas, *J. Amer. Chem. Soc.*, 73, 41 (1951).

(4) (a) D. B. Denny and N. Sherman, *J. Org. Chem.*, 30, 3760 (1965); (b) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 323–325.