

- (6) A. Legendijk and M. Szwarc, *J. Am. Chem. Soc.*, **93**, 5359 (1971).
- (7) P. Balk, G. J. Hooijink, and J. W. J. Schreurs, *Recl. Trav. Chim. Pays-Bas*, **76**, 813 (1957).
- (8) D. Nicholls and M. Szwarc, *Proc. R. Soc. London, Ser. A*, **301**, 223, 231 (1967).
- (9) T. E. Hogen-Esch and J. Smid, *J. Am. Chem. Soc.*, **88**, 307 (1966).
- (10) A. Streitwieser, Jr., J. R. Murdoch, G. Häfelfinger, and C. J. Chang, *J. Am. Chem. Soc.*, **95**, 4248 (1973).
- (11) R. G. Lawler and R. V. Ristagno, *J. Am. Chem. Soc.*, **91**, 1534 (1969).
- (12) R. C. Haddon, M. L. Kaplan, and J. H. Marshall, *J. Am. Chem. Soc.*, **100**, 1235 (1978).
- (13) J. Pople and K. G. Untch, *J. Am. Chem. Soc.*, **88**, 4811 (1966).
- (14) This ion triplet structure is supported by the X-ray crystal structure of anthracene dilithium¹⁵ and cyclooctatetraene dipotassium.¹⁶
- (15) W. E. Rhine, J. Davis, and G. Stucky, *J. Am. Chem. Soc.*, **97**, 2079 (1975).
- (16) J. H. Noordik, Th. E. M. van den Hark, J. J. Mooij, and A. A. K. Klaassen, *Acta Crystallogr., Sect. B*, **30**, 833 (1974); S. Z. Goldberg, K. N. Raymond, C. A. Harmon, and D. H. Templeton, *J. Am. Chem. Soc.*, **96**, 1348 (1974).

Andrew Streitwieser, Jr.,* Carl M. Berke
Karyl Robbers

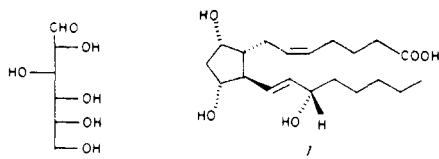
Department of Chemistry, University of California
Berkeley, California 94720

Received August 15, 1978

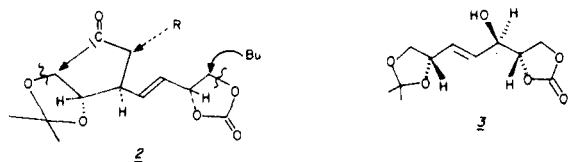
Total Synthesis of Prostaglandin F_{2α} by Chirality Transfer from D-Glucose^{1,2}

Sir:

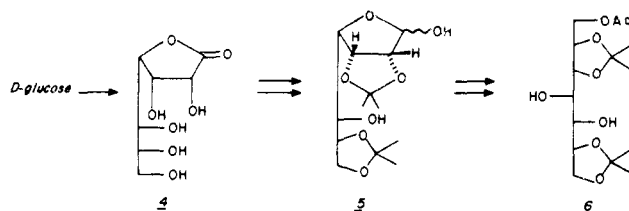
We describe herein the successful construction of prostaglandin PGF_{2α} (**1**) from D-glucose.



The synthetic plan involves the assumption that the transformations shown by arrows on **2** could be effected. A molecule of type **2** should in turn result from C–O → C–C chirality transfer from **3**. It is this molecule which thus became our initial synthetic target.

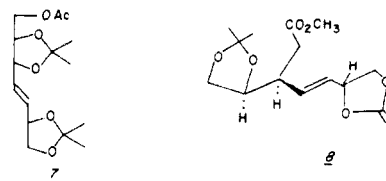


The product of the addition of HCN to D-glucose, the commercially available³ D-glycero-D-guloheptono-1,4-lactone (**4**), was reduced with aqueous sodium borohydride (pH kept at 3–3.5 by simultaneous addition of 10% H₂SO₄) to give (~90% yield) D-glycero-D-guloheptose⁴ from which the required 2,3,6,7-diisopropylidene-D-glycero-D-guloheptose (**5**)

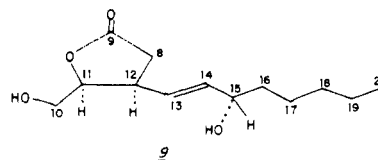


was formed⁵ in 75% yield together with 15% isomeric 3,5,6,7-diisopropylidene derivative.⁶ Reduction to the corresponding diisopropylideneheptitol⁷ (sodium borohydride in

methanol, 10~15 °C, 1.5 h, then acetic acid to pH 7) was followed by acetylation of the primary alcohol to give **6**⁸ (1.2 equiv each of acetic anhydride and pyridine, chloroform, –7 °C, 18 h) and elimination of the adjacent hydroxyl groups by thermolysis of the dimethylformamide cyclic acetal⁹ derived from **6** in the presence of acetic anhydride to produce in ~40% overall yield from **4** the acetoxy trans olefin **7** (purified either



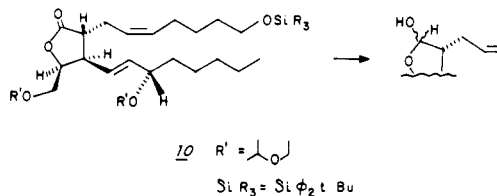
by vacuum distillation or silica gel chromatography): NMR (220 MHz) δ 5.07 (dd, *J* = 6, 16 Hz, 1 H) 5.15 (dd, *J* = 6, 15.5 Hz, 1 H). Freeing of the secondary allylic alcohol required for chirality transfer from C–O to C–C was done by following lines previously laid down in our synthesis of PGA₂ from L-erythrose.^{2a} Removal of the acetate with base was followed by formation of the mixed carbonate (1.5 equiv of methyl chloroformate, pyridine, 0 °C, 2.5 h) which finally led after hydrolysis of the isopropylidene groups (cupric sulfate, aqueous methanol, 24-h reflux) to the necessary terminal five-membered carbonate (addition and removal of benzene–methanol). Transformation of the remaining vicinal glycol to its acetone (acetone, sulfuric acid catalysis, 2 h at room temperature), and then neutralization with ammonia gas and silica gel chromatography (40% ethyl acetate–hexane) now led, in ~54% yield from ~7, to the key intermediate **3**: mp 69–70 °C; [α]_D²⁵ +15.3° (*c* 1.88, CH₃OH); *R*_f 0.46 in ether; NMR δ 1.44 (3 H, s), 1.47 (3 H, s), 3.5 (1 H, br, OH), 3.63 (1 H, dd, *J* = 7, 7 Hz), 6.0 (1 H, ddd, *J* = 1.5, 6.15 Hz). Establishment of the proper chirality at the eventual C₁₂ center was effected by the ortho ester Claisen method¹⁰ to give **8** (80% from silica gel with



CH₂Cl₂), on which the construction of the allylic alcohol side chain was completed essentially by the sequence used in a related case:^{2a} basic hydrolysis of the cyclic carbonate, formation of the primary monotosylate,¹¹ protection of the secondary alcohol with ethyl vinyl ether, and coupling with lithium di-*tert*-butylcuprate (10 equiv, ether, –40 °C, 2 h). The crude cuprate coupling product was then simultaneously deprotected and lactonized to **9** (aqueous sulfuric acid, THF, 15 h, room temperature) obtained from silica gel with 97:3 CH₂Cl₂–CH₃OH in ~35% overall yield from **8**. The sirupy **9** had [α]_D²⁵ +42.6° (*c* 1.55, MeOH) and was a single substance by ¹³C NMR: δ 14.7, 14.47, 31.78, 25.13, 37.09, 71.87, 126.21, 137.44, 40.73, 83.47, 61.39, 177.87, and 35.24 for carbons¹² 20 through 8, respectively. The trans 13,14 double bond in the ¹H NMR showed *J* = 15 Hz.

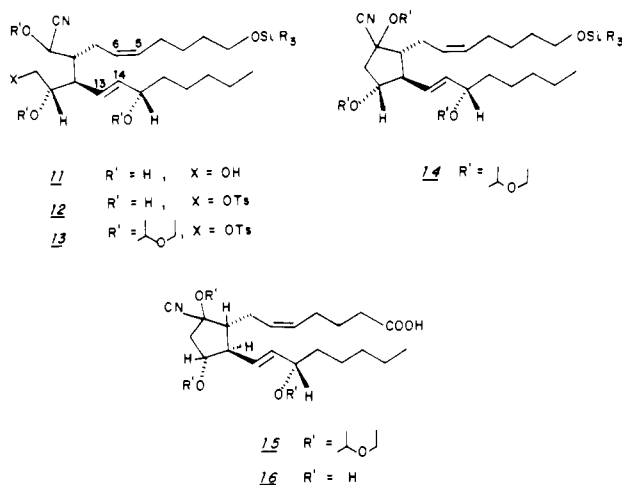
Alkylation of the bis(ethoxyethyl) ether of **9** with the diphenyl *tert*-butylsilyl ether¹³ of 7-bromo-*cis*-5-hepten-1-ol¹⁴ (1.1 equiv of lithium hexamethyldisilazane, THF, –78 °C, and then 3 equiv of bromide in THF–HMPA (final THF–HMPA, ~92:8) at –40 to –20 °C, 2 h) gave 71% of the monoalkylated product **10** (NMR *J*_{8,12} = 16 Hz, (*J*_{11,12} = 7 Hz), together with 13% of the more rapidly eluted (silica gel, 10:5:1–2) cyclohexane–pentane–ethyl acetate dialkylated material.

The construction of the cyclopentanone ring from the lactone was carried out by the protected cyanohydrin method.^{2b,15} Reduction of the lactone of **10** to the hemiacetal (diisobutylaluminum hydride), cyanohydrin formation (HCN, eth-



anol, -10°C), and removal of the ethoxyethyl groups (50% acetic acid-THF, 35°C) gave **11** in which the ^{13}C NMR showed the olefin resonance at δ 128.6, 133.4, 138.0, and 126.3 for carbons 5, 6, 13, and 14, respectively. Tosylation of the primary alcohol (1.5 equiv of TsCl in dry pyridine, -15°C , 1 h; -3°C , 24 h; twice repeated on starting material reisolated from silica gel) now gave **12** in 37% overall yield for the four steps from **10**.

Cyclization was effected by treating the tris(ethoxyethyl) derivative **13** with ~ 6 equiv of potassium hexamethyldisilazane (from potassium hydride-benzene, 5-h reflux) to give, in 72% yield from **12**, the cyclopentane **14** (from silica gel with 10:5:1-2 benzene-pentane-ethyl acetate). Removal of the silyl protecting group with fluoride ion in THF, followed by oxidation of the liberated primary alcohol, first with Collins reagent to the aldehyde and then with silver nitrate-aqueous alcoholic potassium hydroxide, gave **15** in 83% yield from **14**.



We draw attention to the fact that the protected cyanohydrin (cf. **14**) resulting from this particular acyl carbanion equivalent is especially serviceable here because of its compatibility with strong oxidizing agents. Furthermore, the intermediate cyanohydrin resulting from dilute acid treatment is equivalent, in many reactions, to the carbonyl which it masks.

This is important when, as in **16**, the corresponding ketone is particularly unstable.

The synthesis was then easily completed by removal of the three ethoxyethyl protecting groups of **15** (50% acetic acid-THF, 5 h, 40°C) to **16** which was transformed with lithium Selectride (THF, -78°C , 1.5 h) to $\text{PGF}_{2\alpha}$ (**1**, 73% from **15**), characterized fully as its methyl ester (diazomethane). The synthetic substance was completely identical in TLC behavior, infrared, ^1H NMR (220 MHz), ^{13}C NMR, and rotation with natural $\text{PGF}_{2\alpha}$ methyl ester. The transformation of D-glucose into natural $\text{PGF}_{2\alpha}$ had thus been achieved.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their support of this work. We thank Mr. I. Miura for his help in the interpretation of the NMR spectra and Dr. Kathlyn Parker for her important early contributions which led to the eventual design of this synthesis.

References and Notes

- (1) The early part of this synthesis was presented at the Centennial ACS Meeting, New York, N.Y., April 1976.
- (2) For earlier work on prostaglandin synthesis from carbohydrates from this laboratory, cf. (a) G. Stork and S. Raucher, *J. Am. Chem. Soc.*, **98**, 1583 (1976); (b) G. Stork and T. Takahashi, *ibid.*, **99**, 1275 (1977).
- (3) Obtainable from P-L Biochemicals Inc., Milwaukee, Wis.
- (4) M. L. Wolfrom and H. B. Wood, *J. Am. Chem. Soc.*, **73**, 2933 (1951). The crude product ($\sim 90\%$ yield) melted at $171-175^\circ\text{C}$ and was pure enough for further transformation.
- (5) J. S. Brimacombe and L. C. N. Tucker, *J. Chem. Soc. C*, 562 (1968). We used ammonia gas to neutralize the reaction mixture.
- (6) The ratio was determined by LC (Porasil A, 5% 2-propanol in hexane; **5** has the lower retention time). It is not necessary to separate these isomers, since only the dimethylformamide acetal derived from **6** can undergo transformation to the olefin **7**.
- (7) We thank Mr. S. L. Buchwald for his contribution to the design of this step.
- (8) All substances gave spectral (IR, NMR) and, in selected cases, mass spectra in agreement with their assigned structure.
- (9) F. W. Eastwood, K. J. Harrington, J. S. Josan, and J. L. Pura, *Tetrahedron Lett.*, 5223 (1970).
- (10) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Am. Chem. Soc.*, **92**, 741 (1970).
- (11) Tosylation was carried out, more conveniently than in ref 2a, for 10 h at 0°C with 1.2 equiv of acid chloride.
- (12) The numbering used shows the position of the carbons in the eventual prostaglandin.
- (13) S. Hanessian and P. Lavalle, *Can. J. Chem.*, **53**, 2975 (1975).
- (14) Prepared by LiAlH_4 reduction of the 1-ethoxyethyl derivative of methyl 7-hydroxy-*cis*-5,6-heptenoate (cf. J. Martel and E. Toromanoff, *Chem. Abstr.*, **76**, 24712 (1972)), protection of the resulting primary alcohol with *tert*-butyldiphenylchlorosilane, deprotection (acetic acid-water) of the allylic hydroxyl, and, finally, reaction with triphenylphosphine-carbon tetrabromide.
- (15) G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **92**, 5286 (1971).
- (16) We are pleased to thank Dr. John Pike of the Upjohn Co. for a sample of Natural $\text{PGF}_{2\alpha}$.

Gilbert Stork,* Takashi Takahashi
 Isao Kawamoto, Toshio Suzuki

Department of Chemistry, Columbia University
 New York, New York 10027

Received July 28, 1978