(6) A. Lagendijk and M. Szwarc, *J. Am. Chem. Soc.*, **93**, 5359 (1971).
(7) P. Balk, G. J. Hoijtink, 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. Häfelinger, 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 dilithium[15] 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).

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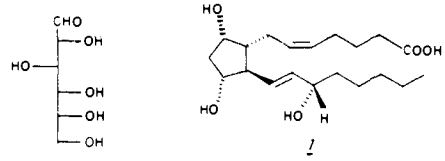
## Total Synthesis of Prostaglandin $F_{2\alpha}$ by Chirality Transfer from D-Glucose[1,2]

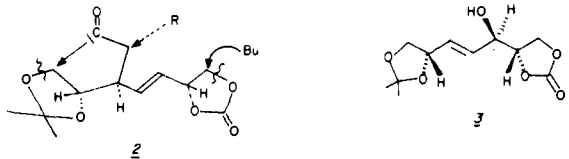
*Sir:*

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



**1**

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.

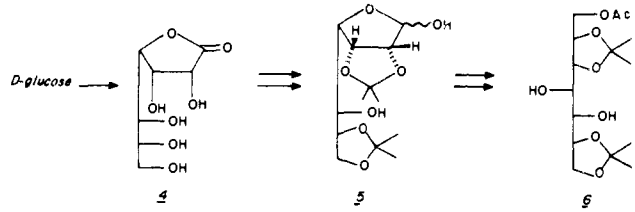


**2**



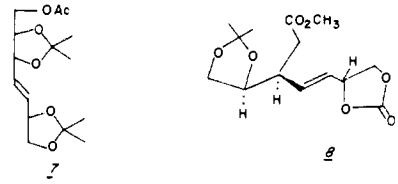
**3**

The product of the addition of HCN to D-glucose, the commercially available[3] 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% $H_2SO_4$) to give (~90% yield) D-glycero-D-guloheptose[4] from which the required 2,3,6,7-diisopropylidene-D-glycero-D-guloheptose (**5**)



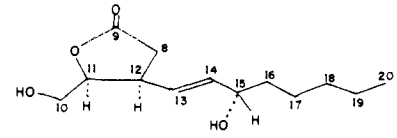
**4** **5** **6**

was formed[5] in 75% yield together with 15% isomeric 3,5,6,7-diisopropylidene derivative.[6] Reduction to the corresponding diisopropylideneheptitol[7] (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 cylic acetal[9] derived from **6** in the presence of acetic anhydride to produce in ~40% overall yield from **4** the acetoxy trans olefin **7** (purified either



**7** **8**

by vacuum distillation or silica gel chromatography): NMR (220 MHz) $\delta$ 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 $PGA_2$ 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 acetonide (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; $[\alpha]^{25}_D$ +15.3° ($c$ 1.88, $CH_3OH$); $R_f$ 0.46 in ether; NMR $\delta$ 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 $C_{12}$ center was effected by the ortho ester Claisen method[10] to give **8** (80% from silica gel with



**9**

$CH_2Cl_2$), 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 dibutylcuprate (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 $CH_2Cl_2$-$CH_3OH$ in ~35% overall yield from **8**. The sirupy **9** had $[\alpha]^{25}_D$ +42.6° ($c$ 1.55, MeOH) and was a single substance by $^{13}C$ NMR: $\delta$ 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 carbons[12] 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 ether[13] of 7-bromo-*cis*-5-hepten-1-ol[14] (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 (diisobutylaluminium hydride), cyanohydrin formation (HCN, eth-

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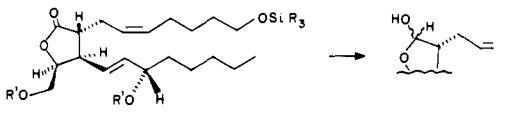
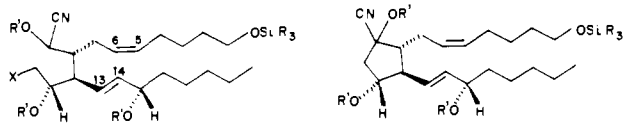


10 R' = THP

$SiR_3 = Si\phi_2 t\text{-}Bu$

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.**



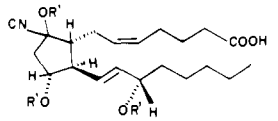
11 R' = H, X = OH

12 R' = H, X = OTs

13 R' = THP, X = OTs



14 R' = THP



15 R' = THP

16 R' = H

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 $PGF_{2\alpha}$ (**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 $PGF_{2\alpha}$ methyl ester. The transformation of D-glucose into natural $PGF_{2\alpha}$ had thus been achieved.

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## 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 (~90% yield) melted at 171–175 °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 $PGF_{2\alpha}$.

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