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PROSTAGLANDINS AND CONGENERS XII.[1]

THE SYNTHESIS OF dℓ-ERYTHRO AND dℓ-THREO-15,16-DIHYDROXYPROSTAGLANDINS

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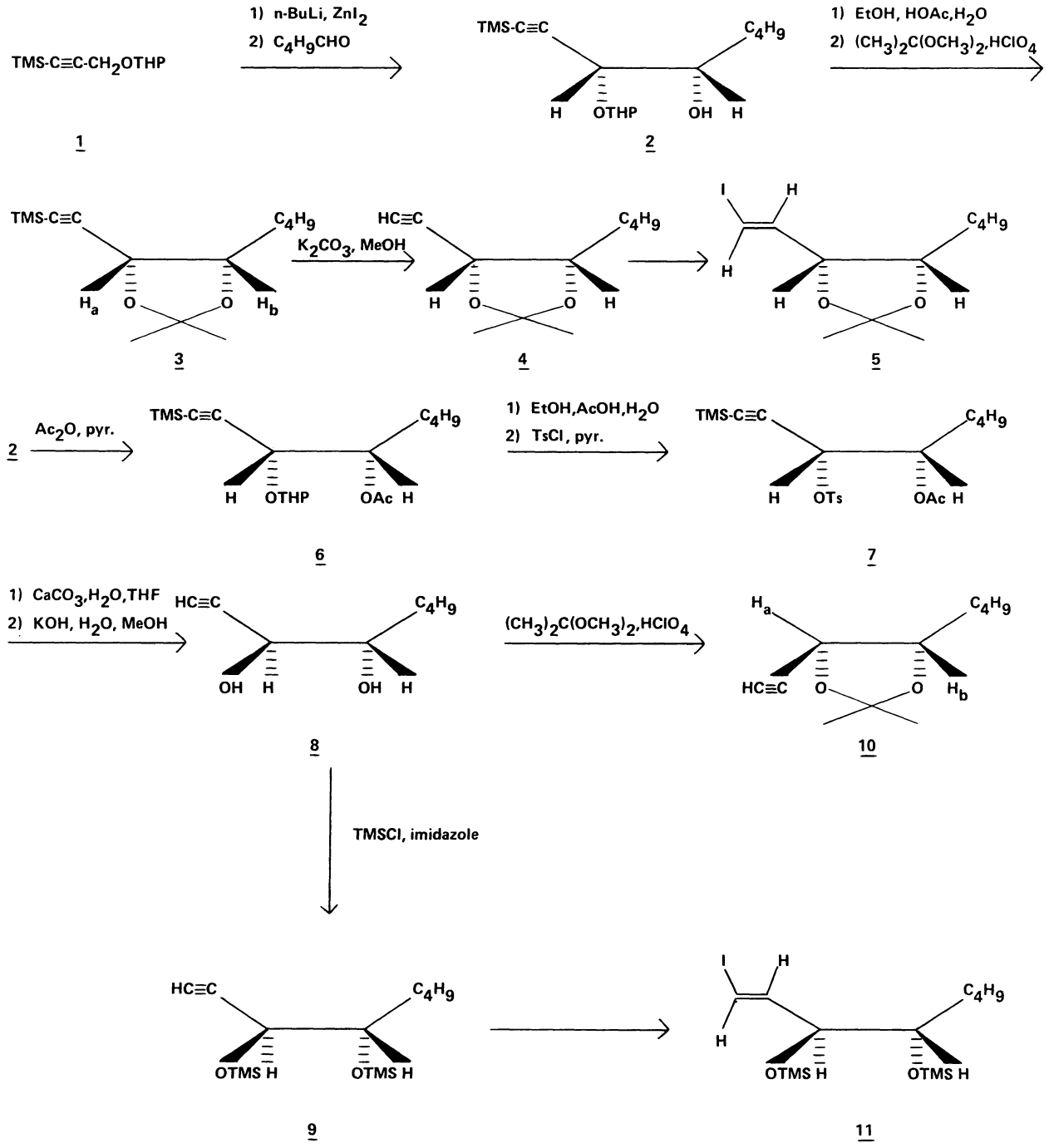
An efficient first synthesis of all four dℓ-16-hydroxy-PGE_2 racemates via conjugate addition of functionalized vinyl cuprates to a cyclopentenone is presented. Compounds in the PGA_2 and $PGF_{2\alpha}$ series are also described.

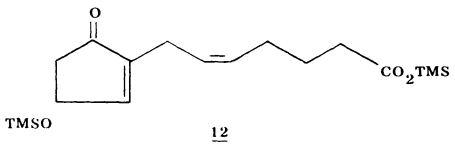
During the past several years our laboratory has been involved in the synthesis of prostaglandin congeners wherein the 15-hydroxy function is shifted to other positions along the β-chain. In previous reports we described the synthesis of congeners in which the hydroxy function has been placed at the C_{13}, C_{16}, C_{17} or C_{20} positions.[2] In particular, it was observed that a C_{16}-hydroxy group was consistent with important biological activity.[2] Accordingly it was of interest to prepare a congener containing both a C_{15} and C_{16} hydroxy group.

Our synthetic approach relies on the conjugate addition of appropriately functionalized vinyl cuprate reagents to the cyclopentenone 12. The precursor vinyl iodides 5 and 11 were prepared as outlined below.[3] The reaction of 1[4] and valeraldehyde gave erythro 2 as the major stereoisomer.[5] Removal of the THP group [EtOH:AcOH:H_2O, 2:1:1, 100°, 3 hr] followed by acetonide formation [$(CH_3)_2C(OCH_3)_2$, $HClO_4$, RT, 30 min] furnished 3. Hydrolysis of the TMS group [K_2CO_3, MeOH, 100°, 1 hr] provided 4, which after distillation (bp 103-106°/13 mm) was converted to erythro vinyl iodide 5 by the diisoamylborane procedure.[7]

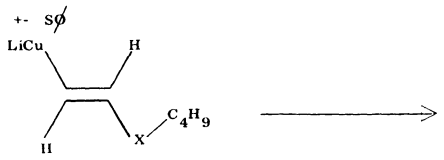
For the synthesis of the vinyl iodide of the threo series, alcohol 2 was acetylated [Ac_2O, pyridine, 100°, 15 hr] to give 6. Removal of the THP group [EtOH:AcOH:H_2O, 2:1:1, 100°, 3 hr] and tosylation [TsCl, pyridine, 15 hr, RT] gave 7. Solvolysis of tosylate 7 [$CaCO_3$, H_2O, THF, reflux, 96 hr], followed by hydrolysis [KOH, H_2O, MeOH] of the resulting mixture of threo-acetates gave the threo-acetylenic diol 8, which was protected either as the bis-TMS derivative 9 [TMSCl, imidazole, DMF] or the acetonide 10 [$(CH_3)_2C(OCH_3)_2$, $HClO_4$]. Conversion of 9 to vinyl iodide 11 was accomplished by the diisoamylborane procedure.[7]

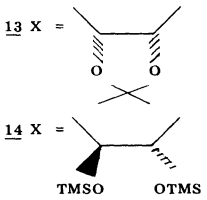
The vinyl iodides 5 and 11 were each exchanged with two equivalents of t-butyl lithium at -78° in ether to give the respective vinyl lithium derivatives, which on treatment with a solution of copper (I) thiophenoxide gave the corresponding vinyl cuprate reagents 13 and 14.[8] Conjugate addition of these vinyl cuprate reagents to the bis-TMS protected cyclopentenone 13[9] followed by removal of the protecting groups and silica-gel chromatography gave from 13 the erythro epimers 15 and 16 and from 14 the threo epimers 17 and 18.

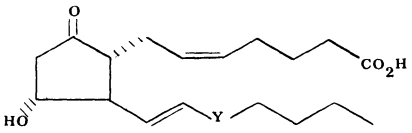

TMS-C≡C-CH2OTHP
1) n-BuLi, ZnI2
2) C4H9CHO
1
TMS-C≡C
C4H9
H OTHP OH H
2
1) EtOH, HOAc,H2O
2) (CH3)2C(OCH3)2,HClO4
TMS-C≡C
C4H9
Ha O O Hb
3
K2CO3, MeOH
HC≡C
C4H9
H O O H
4
I H
H
C4H9
H O O H
5
2
Ac2O, pyr.
TMS-C≡C
C4H9
H OTHP OAc H
6
1) EtOH,AcOH,H2O
2) TsCl, pyr.
TMS-C≡C
C4H9
H OTs OAc H
7
1) CaCO3,H2O,THF
2) KOH, H2O, MeOH
HC≡C
C4H9
OH H OH H
8
(CH3)2C(OCH3)2,HClO4
Ha
C4H9
HC≡C O O Hb
10
TMSCl, imidazole
HC≡C
C4H9
OTMS H OTMS H
9
I H
H
C4H9
OTMS H OTMS H
11

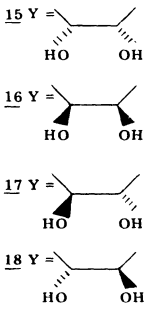

O
CO2TMS
TMSO

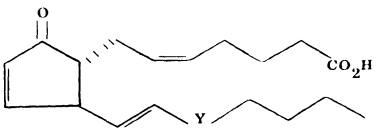
12

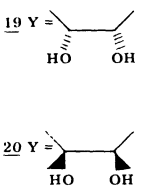

+- Sφ
LiCu
H
H
X
C4H9

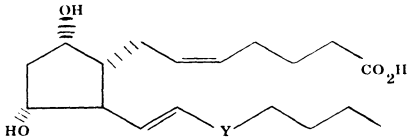

13 X =
O
O
14 X =
TMSO
OTMS

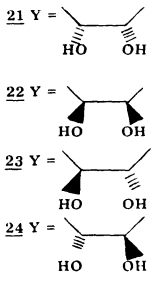

O
CO2H
HO
Y


15 Y =
HO
OH
16 Y =
HO
OH
17 Y =
HO
OH
18 Y =
HO
OH


O
CO2H
Y


19 Y =
HO
OH
20 Y =
HO
OH


OH
CO2H
HO
Y


21 Y =
HO
OH
22 Y =
HO
OH
23 Y =
HO
OH
24 Y =
HO
OH

Treatment of 15 and 16 with 1.5N hydrochloric acid in THF gave the respective PGA_2 analogs 19 and 20; reduction of 15-18 with lithium perhydro-9b-boraphenalyhydride gave the respective $PGF_{2\alpha}$ derivatives 21-24.

The PGE_2 analogs 15-18 and the $PGF_{2\alpha}$ analogs 21-24 all show prostaglandin-like smooth muscle stimulating activity in the gerbil colon assay[10] in the range 0.5%-14% of ℓ-PGE_1.

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2. (a) A. Wissner, submitted for publication; (b) M. B. Floyd, R. E. Schaub, and M. J. Weiss, Prostaglandins, 10, 289 (1975).
3. Satisfactory proton magnetic resonance, infrared, and C,H analytical or high resolution mass spectral data were obtained for the new compounds reported herein.
4. (a) H. Chwastek, R. Epsztein, and N. Le Goff, Tetrahedron, 29, 883 (1973); (b) H. Chwastek, N. Le Goff, R. Epsztein, and M. Baran-Marszak, Tetrahedron, 30, 603 (1974).
5. The erythro configuration of 2 was assigned on the basis of literature analogy[4a] and on a comparison of the NMR spectra of acetonides 4 [$\delta^{CDCl_3}_{TMS}$, 4.72 (dd, 1H, Ha, J_{ab}=5.4 Hz); 4.08 (m, 1H, H_b)] and 10 [$\delta^{CDCl_3}_{TMS}$, 4.20 (dd, 1H, H_a, J_{ab}=8.0 Hz); 4.02 (m, 1H, H_b)] with model compounds.[6]
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9. Compound 12 was prepared from the unprotected cyclopentenone [M. B. Floyd, Syn. Comm., 4, 317 (1974)] using hexamethyldisilazane-trimethylsilylchloride in pyridine.
10. J. R. Weeks, J. R. Schultz, and W. E. Brown, J. Appl. Physiol., 25 (6), 783 (1968).

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