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SYNTHESIS OF 11-DESOXY-PROSTAGLANDINS

Pierre Crabbé and Angel Guzmán
Research Laboratories, Syntex, S. A.,
Apartado Postal 10-820, Mexico 10, D. F., Mexico

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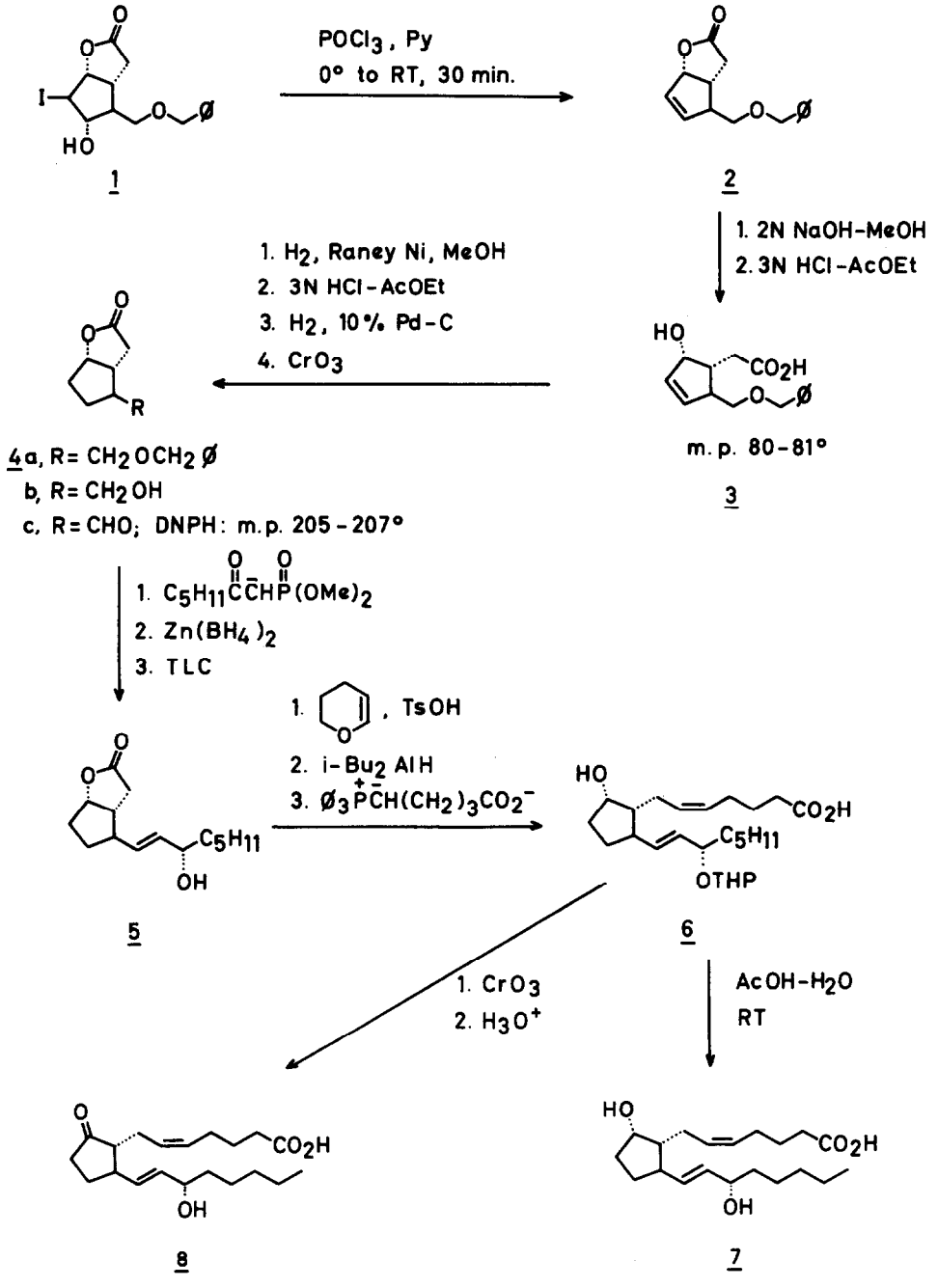
For some time we have been engaged in a research program having as its main objective the chemical synthesis of modified prostaglandins[1]. Among the numerous total syntheses now available, one reported by the Harvard group[2] was of particular interest to us, because it is stereospecific and offers substantial flexibility for the preparation of modified prostaglandins. We wish to report a synthesis of dl-11-desoxy-$PGF_{2\alpha}$ (7) and dl-11-desoxy-PGE_2 (8), which uses the known bicyclic iodolactone (1)[2] as the starting material (see Chart).

Reaction of the iodohydrin (1) with freshly distilled phosphorus oxychloride in pyridine solution first at 0° and then at room temperature without reducing salt afforded the bicyclic olefin (2) [ν_{max} 1770, 1615 cm^{-1}, n.m.r. 6.0 ppm (m, 2 vinylic H)] (92% yield). The conversion of (1) into (2) is a highly efficient elimination performed under mild conditions, and it has been found to be a method of general applicability for olefin synthesis[3].

In order to prevent hydrogenolysis of the allylic hydroxyl in (2) during the reduction of the double bond, the lactone group was opened by treatment with 2N methanolic sodium hydroxide and the salt was then carefully neutralized with 3N hydrochloric acid in ethyl acetate to pH 6, thus affording the crystalline hydroxy-acid (3) [ν_{max} 3500, 1700 cm^{-1}] (97% yield). Catalytic reduction of (3) with Raney nickel in methanol followed by brief exposure to acid provided the saturated bicyclic lactone (4a) [ν_{max} 1770 cm^{-1}] (94% yield). Treatment of (4a) in an hydrogen atmosphere with 10% palladium on carbon in dimethoxyethane in the presence of a trace of perchloric acid caused cleavage of the benzyl ether, thus affording the alcohol (4b) [ν_{max} 3350, 1770 cm^{-1}, n.m.r. 2.2 ppm (OH)] (97% yield). Oxidation of (4b) with Collins' reagent[4] gave the aldehyde (4c) [ν_{max} 2680, 1770, 1705 cm^{-1}, n.m.r. 9.71 ppm (aldehydic H)] (99% yield), identified as its crystalline 2,4-dinitrophenylhydrazone [ν_{max} 1770, 1620, 1580 cm^{-1}].


POCl3, Py
0° to RT, 30 min.
1
2
1. 2N NaOH-MeOH
2. 3N HCl-AcOEt
3
m.p. 80-81°
1. H2, Raney Ni, MeOH
2. 3N HCl-AcOEt
3. H2, 10% Pd-C
4. CrO3
4a, R= CH2OCH2Ø
b, R= CH2OH
c, R= CHO; DNPH: m.p. 205-207°
1. C5H11COCHP(OMe)2
2. Zn(BH4)2
3. TLC
5
1. , TsOH
2. i-Bu2AlH
3. Ø3PCH(CH2)3CO2-
6
1. CrO3
2. H3O+
AcOH-H2O
RT
8
7

The aldehyde (4c) was then submitted to the sequence of reactions (see Chart) reported previously for the synthesis of $PGF_{2\alpha}$[2].

The separation of the required 15(S)-alcohol derivative (5) [ν_{max} 3350, 1770, 970 cm^{-1}, n.m.r. 0.89 (CH_3), 3.7 (OH), 5.5 (m, 4 vinylic H)], was effected by preparative TLC. The undesired 15(R)-alcohol isomer formed after zinc borohydride reduction of the enone [λ_{max} 226 nm (log ε 4.2), ν_{max} 1770, 1670, 1625, 970 cm^{-1}, n.m.r. 0.89 (CH_3), 6.19 and 6.79 ppm (dd, J_1 6 Hz, J_2 16 Hz, trans olefin at C_{13})], resulting from alkylation of (4c) with dimethyl 2-oxoheptylphosphonate, could be recycled by manganese dioxide oxidation in tetrahydrofuran.

Whereas mild treatment of the 15α-ether derivative (6) [ν_{max} 3350, 1710, 960 cm^{-1}, n.m.r. 0.89 (CH_3), 5.48 (m, 4 vinylic H), 6.19 ppm (9α-OH, CO_2H)] with aqueous acetic acid afforded dl-11-desoxy-$PGF_{2\alpha}$ (7) [colorless oil, ν_{max} 3350, 1710, 960 cm^{-1}, n.m.r. 0.89 (CH_3), 4.06 (15α-OH), 5.5 (m, 4 vinylic H), 6.19 ppm (9α-OH,CO_2H)], Jones' oxidation[5] of (6) followed by brief exposure to acid provided dl-11-desoxy-PGE_2 (8) [colorless oil, ν_{max} 3350, 1745, 1710, 970 cm^{-1}, n.m.r. 0.89 (CH_3), 4.05 (15α-OH), 5.5 (m, 4 vinylic H), 6.19 ppm (CO_2H)], thus completing the synthesis of these 11-desoxy primary prostaglandins[6].

References

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6. After completion of our work, Professor E.J. Corey kindly informed us of a method similar to that mentioned above for the transformation of the iodohydrin (1) into the olefin (2).