Communications to the Editor

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A SYNTHESIS OF (±)-6,9α-METHANOPROSTAGLANDIN I_3, A STABLE ANALOG OF PROSTAGLANDIN I_3

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6,9α-Methanoprostaglandin I_3, a stable analog of prostaglandin I_3, has been synthesized using a new method for the stereoselective introduction of the 15α-hydroxy group.

KEYWORDS —— prostacyclin analog; stereoselective synthesis; methanoprostaglandin I_3; phenylsulfenyl chloride

Prostaglandin I_3 is a potent inhibitor of platelet aggregation and is unstable due to the enol ether portion. The synthesis of prostaglandin I_3 has already been reported by Nidy and Johnson.[1] We herein describe a synthesis of a stable carba-analog of prostaglandin I_3 using a new and stereoselective method for the introduction of the 15α-hydroxy function, which saves tedious chromatographic separation of 15α- and 15β-hydroxy isomers.

A general plan of our stereoselective introduction of the 15α-hydroxy group is depicted in retrosynthetic analysis in Chart 1. The sulfide (IV) serves to form the 15α-alcohol (V) selectively via a 2,3-sigmatropic rearrangement. The sulfide (IV) is in turn accessible by cis-olefination of the aldehyde (III), which is derived from the vinyl ether (II) by an addition of phenylsulfenyl chloride.

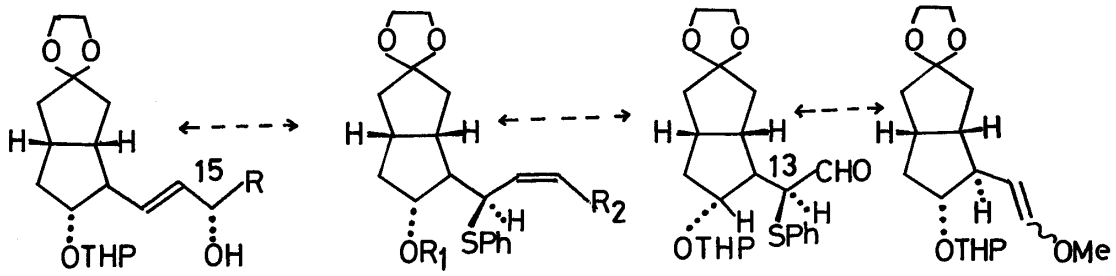
The key intermediate (II), IR(liq) cm^{-1}: 1665, PMR($CDCl_3$) δ: 3.50, 3.55 (a pair of singlets, OMe) was synthesized by treatment of the aldehyde (I)[2] with the ylide $Ph_3P{=}CHOMe$ in dimethyl sulfoxide in 75% yield.

The stereoselective electrophilic addition of phenylsulfenyl chloride to an asymmetrically substituted allylic double bond (enol ether) in the compound (II) proceeded smoothly. Treatment of II in toluene with phenylsulfenyl chloride at -78°C in the presence of powdered potassium carbonate, followed by treatment with 10% sodium hydrogen carbonate solution (two phase) yielded the aldehyde (III)[3] stereoselectively in 91% yield.[4] IR(liq) cm^{-1}: 1585, 1710, 2720, PMR($CDCl_3$) δ: 3.91(OCH_2CH_2O), 7.32(aromatic protons), 9.32(CHO).

The stereochemistry at C-13 (PG numbering) in the aldehyde (III) was determined by the following reactions leading to the 15α-alcohol (V,R=C_5H_{11}).

Treatment of the aldehyde (III) with the ylide, $Ph_3P{=}CHC_5H_{11}$ in tetrahydrofuran/dimethyl sulfoxide (8/1) at -78°C and then ambient temperature afforded the

sulfide (IV, R_1=THP, R_2=C_5H_{11}) in 50% yield. IR(liq) cm^{-1}: 1585, PMR($CDCl_3$) δ: 0.83(CH_3).



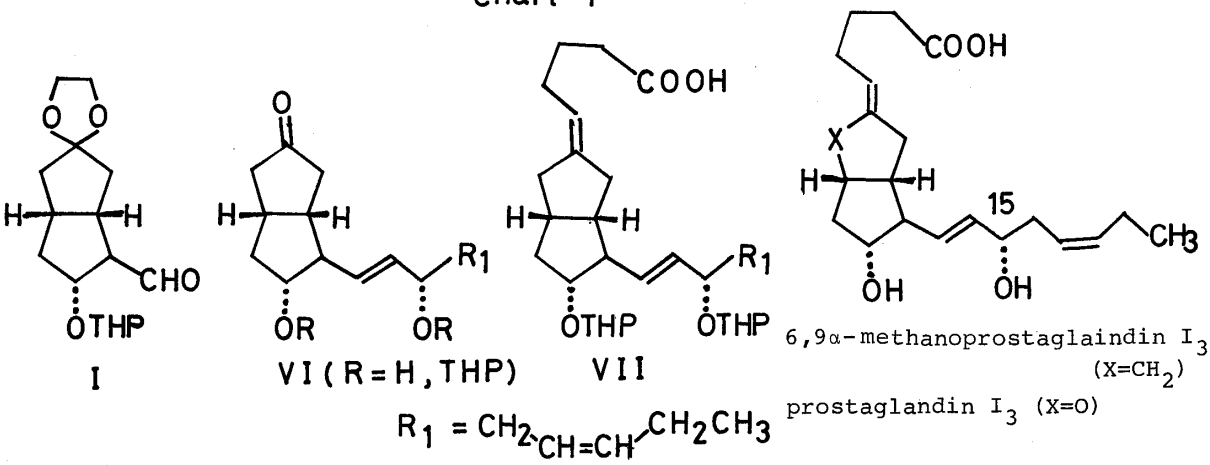
V IV III II

$R = C_5H_{11}$, (Z)-$CH_2CH=CHCH_2CH_3$

R_1=H, THP

R_2=C_5H_{11}, (Z)-$CH_2CH=CHCH_2CH_3$

Chart 1



I VI (R=H, THP) VII

6,9α-methanoprostaglaindin I_3 (X=CH_2)

prostaglandin I_3 (X=O)

R_1 = $CH_2CH=CHCH_2CH_3$

Deprotection of IV(R_1=THP, R_2=C_5H_{11}) with aqueous acetic acid gave the alcohol (IV, R_1 = H, R_2=C_5H_{11}). The IR(liq) spectrum of IV(R_1=H, R_2=C_5H_{11}) has no signal of 970 cm^{-1} characteristic of the trans(E) double bond. Moreover the coupling constant (J=10.5Hz) of the olefinic protons in the PMR($CDCl_3$, 400MHz, decoupling experiment)[5] supported the cis(Z) structure of the double bond in the alcohol (IV, R_1=H, R_2=C_5H_{11}) and hence that of the sulfide (IV, R_1=THP, R_2=C_5H_{11}). Treatment of the sulfide (IV, R_1=THP, R_2=C_5H_{11}) with m-chloroperbenzoic acid in methanol at -30°C, followed by the addition of trimethyl phosphite at -30°C and then ambient temperature yielded the 15α-hydroxy compound (V, R=C_5H_{11}) in 89% yield,[6] which was identified with an authentic sample prepared previously (TLC, IR, PMR, MS).[2]

Having in hand the aldehyde (III) with a desirable stereochemistry for the introduction of the 15α-hydroxy group we then converted the aldehyde (III) to 6,9α-methanoprostaglandin I_3 by the following process.

The Wittig reaction of III with the ylide (Z)-$Ph_3P=CHCH_2CH=CHCH_2CH_3$[7] by the method described above yielded the sulfide (IV, R_1=THP, R_2=(Z)-$CH_2CH=CHCH_2CH_3$) IR(liq) cm^{-1}: 1585, PMR($CDCl_3$) δ: 0.90(3H, t, J=7Hz, CH_3), 4.8-5.6 (olefinic protons), in 73% yield. Oxidation of IV(R_1=THP, R_2=(Z)-$CH_2CH=CHCH_2CH_3$) with m-chloroperbenzoic acid, followed by addition of trimethyl phosphite afforded 15α-hydroxy compound (V, R=(Z)-$CH_2CH=CHCH_2CH_3$) in 95% yield. IR(liq) cm^{-1}: 3450,

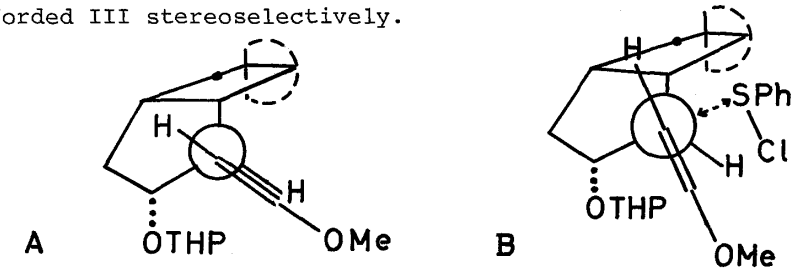
PMR($CDCl_3$) δ: 0.95(CH_3), 3.86(OCH_2CH_2O), 4.64(OCHO), 5.2-5.7(4H, m, olefinic protons).

Treatment of V(R=(Z)-$CH_2CH=CHCH_2CH_3$) with aqueous acetic acid at 40°C yielded the diol(VI, R=H), IR(liq) cm^{-1}: 970, 1710, 3380, PMR($CDCl_3$) δ: 0.97(3H, t, CH_3), 3.7-4.3(m, >CHOHx2), 5.1-5.8(m, olefinic protons). Tetrahydropyranylation of VI(R=H) in methylene chloride with dihydropyran and p-TsOH at 5°C gave the ditetrahydropyranyl compound (VI, R=THP), IR(liq) cm^{-1}: 970, 1740. The Wittig reaction of VI (R=THP) with the ylide $Ph_3P=CHCH_2CH_2CH_2COONa$ in dimethyl sulfoxide and separation of Δ^5-isomers by silica gel column chromatography yielded the acid (VII, more polar)[8] and the 5(Z)-isomer of the acid (VII). Treatment of the acid (VII) with aqueous acetic acid at room temperature for 20 hours afforded 6,9α-methanoprostaglandin I_3 in good yield, IR(liq) cm^{-1}: 970, 1705, 3350, PMR($CDCl_3$) δ: 0.97(3H, t, J=7Hz, CH_3), 3.70(1H, br, >CHOH), 4.10(1H, br, >CHOH), 5.1-5.8 (5H, m, olefinic protons).

6,9α-Methanoprostaglandin I_3 was a potent inhibitor for platelet aggregation induced by collagen(rabbit).

REFERENCES AND NOTES

1) E.G. Nidy, and R.A. Johnson, Tetrahedron Lett., 1978, 2375.
2) K. Kojima, and K. Sakai, Tetrahedron Lett., 1978, 3743.
3) Similar treatment of II with phenylsulfenyl chloride, followed by treatment with 10% $NaHCO_3$ in D_2O yielded, without incorporation of deuterium, the same aldehyde (III).
4) The stereoselectivity might be explained as follows: The stable conformation of II is assumed to be A (see: G. Schmid, T. Fukuyama, K. Asaka, and Y. Kishi, J. Am. Chem. Soc., 101, 259 (1979)). Therefore the addition reaction of phenylsulfenyl chloride would take place from the sterically less hindered side (via transition structure B) to give β-chloro-β-methoxyphenyl sulfide intermediate, which upon hydrolysis (directly and/or via episulfonium ion) afforded III stereoselectively.



5) We thank Mr. Kuwano for valuable discussion on PMR analysis.
6) The stereospecificity for the introduction of 15α-hydroxy group (II to V) is 92-95% based on high pressure liquid chromatography.
7) (Z)-$Ph_3P=CHCH_2CH=CHCH_2CH_3$ was prepared from the corresponding phosphonium iodide (Z)-$CH_3CH_2CH=CHCH_2CH_2P^+Ph_3\ I^-$, mp 158°C, which was synthesized from 3(Z)-hexen-1-ol by the following: i) Tosylation with TsCl and pyridine; ii) Iodination with NaI in acetone; iii) Reaction with Ph_3P in acetonitrile.
8) The stereochemistry of the double bond at C-5 was assigned on the basis of TLC behavior. See reference 2. The ratio of 5E- to 5Z-isomer is about 2 to 1.

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