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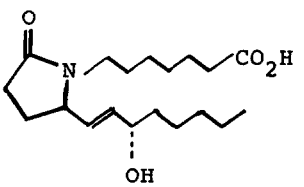
AZAPROSTANOIDS I. SYNTHESIS OF (RAC)-8-AZA-11-DEOXY-15-DEOXY-16-HYDROXY-16-METHYLPROSTAGLANDINS[1]

Chia-Lin J. Wang
Central Research and Development Department, Experimental Station
E. I. du Pont de Nemours and Company
Wilmington, Delaware 19898

ABSTRACT: A total synthesis of the title compounds by employing a stereoselective Wittig reaction is described.

In recent years a considerable number of azaprostaglandin[2] and azaprostacyclin[3] analogs have been synthesized. One of the most interesting is 8-aza-11-deoxy PGE_1 (1) because of its prostaglandin-like activities[4]. In addition, it has only two asymmetric centers in comparison to four in natural PGE_1. As part of our continuing interest in azaprostaglandins, we wanted to



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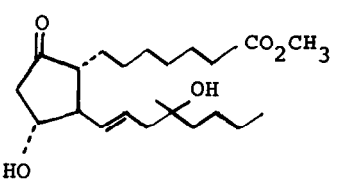
search for analogs which would exhibit anti-ulcer or anti-asthma activity. Recently 15-deoxy-16-hydroxy PGE analogs have been reported to be more potent than natural prostaglandins as gastric antisecretory agents and bronchodilators[5]. For example, 15-deoxy-16-hydroxy-16-methyl PGE_1 methyl ester (2) was found to be 40 times more potent than PGE_1 itself as a gastric antisecretory agent and was reported in U.S. clinical trials. Therefore, we targeted the title compounds 3 and 4 for synthesis in the hope that they might have similar biological activities as the all carbon analog.



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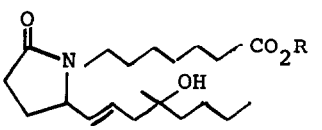

3, R = H
4, R = CH_3

Most synthetic routes leading to the 15-deoxy-16-hydroxy PGE analogs involve conjugate addition of the lithiocuprates derived from the appropriately functionalized vinylstannanes 5 or vinyliodides 6 to cyclopentenones 7. We

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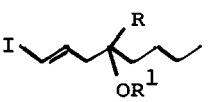

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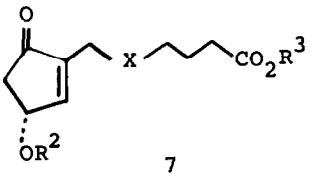

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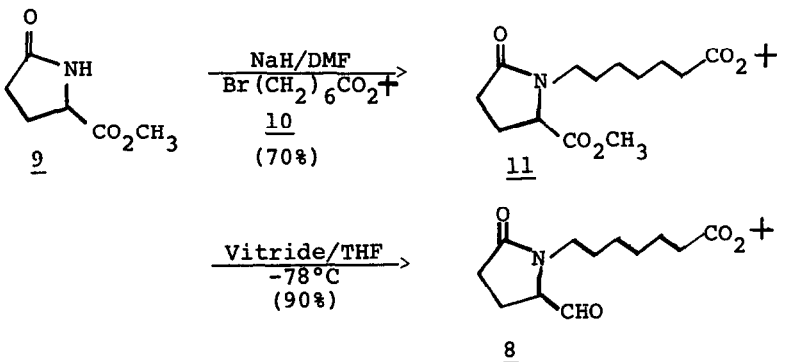
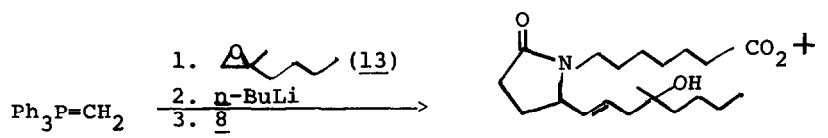
wish to report a new methodology for introducing the 15-deoxy-16-hydroxy-16-methyl side chain as exemplified in the following synthesis of the aza PGE_1 analogs 3 and 4.

Compound 3 could be derived from aldehyde 8 which was readily prepared by the following transformations[6]. Racemic methyl pyroglutamate (9) was alkylated with t-butyl 7-bromoheptanoate (10) in the presence of sodium hydride in dimethylformamide to give 11[7]. Vitride (0.6 equiv.) at -78°C selectively reduced the methyl ester 11 to aldehyde 8[7].



9 → (NaH/DMF, Br(CH$_2$)$_6$CO$_2$+ 10, 70%) → 11 → (Vitride/THF, -78°C, 90%) → 8

Application of the recently reported method for the selective preparation of trans-homoallylic alcohols[8] allowed the introduction of the lower side chain in a one-pot reaction. Thus, methylenetriphenylphosphorane[8] (12) was reacted with 2-methyl-1-hexene oxide (13) at 0°C to room temperature. The product was treated with one equivalent of n-butyllithium to yield a dark red ylide solution. This was cooled to -40°C and treated with a solution of aldehyde 8 in tetrahydrofuran. After 17 hrs at ambient temperature the desired olefin 14[7] was obtained in 70% yield after purification. The stereochemistry of the double bond was confirmed as trans by the coupling constant (ca. 17 Hz) in NMR spectrum. The t-butyl ester 14 was hydrolyzed by treatment



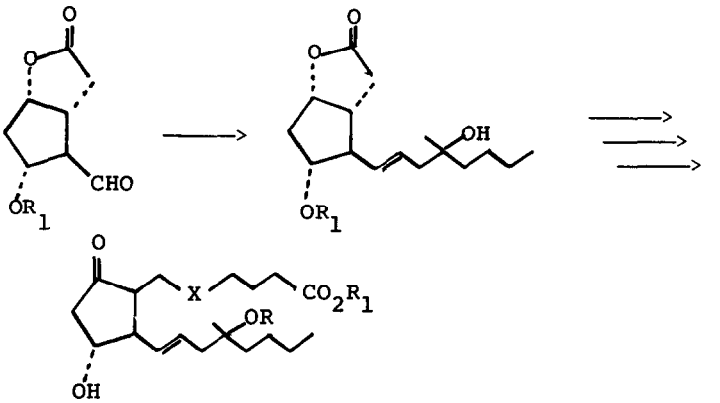
12 → (1. (13); 2. n-BuLi; 3. 8) → 14

with 85% H_3PO_4[9] in small amount of tetrahydrofuran to give 95% yield of 3[7] which, upon treatment with diazomethane, afforded 4[7].

It should be noted that by utilizing optically active 13 and separating the diastereomers, we would be able to synthesize optically active 3 and 4.

Compounds 3 and 4 show ca. 30% protection at 2 mg/kg (P.O.) in cyto-protection test and ca. 15% protection at 0.5 mg/kg (I.P.) in histamine-challenge anti-bronchoconstriction screening.[10]

It should also be noted that by applying this one-pot Wittig reaction it would be possible to synthesize the 15-deoxy-16-hydroxy-16-methyl PGE analogs from Corey's aldehyde. Thus one could avoid several steps involved



in preparing 5 or 6 as well as the tedious generation of the corresponding cuprates which have been used in the synthesis of the 15-deoxy-16-hydroxy-16-methyl PGE analogs from 7.

References and Notes

1. Contribution No. 2984 from the Central Research and Development Department.
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6. Ref. 4 (a).

7. 11: IR (neat): 1750, 1740, 1700 cm^{-1}; NMR ($CDCl_3$): δ 3.76 (s, 3H), 1.46 (s, 9H).
8: IR (neat): 1720, 1660, 1640 (sh) cm^{-1}; NMR ($CDCl_3$): δ 9.58 (d, J = 2.5 Hz, 1H), 1.45 (s, 9H).
14: IR (CH_2Cl_2): 3400, 1745, 1680 cm^{-1}; NMR ($CDCl_3$): δ 5.73 (dt, J = 17 & 7 Hz, 1H), 5.30 (dd, J = 17 & 7 Hz, 1H), 1.43 (s, 9H), 1.16 (s, 3H), 0.92 (t, 3H).
3: IR (CH_2Cl_2): 3600-2500 (br), 1750-1650 (br) cm^{-1}; NMR ($CDCl_3$): δ 8.14 (br, 2H, $-CO_2H$ & -OH), 5.73 (dt, J = 17 & 7 Hz, 1H), 5.30 (dd, J = 17 & 7 Hz, 1H), 1.16 (s, 3H), 0.91 (t, 3H); Ms: m/e 353.3583 (M^+). Calcd. for $C_{20}H_{35}O_4N$: 353.2564.
4: IR (CH_2Cl_2): 3600, 3400, 1740, 1680 cm^{-1}; NMR ($CDCl_3$): δ 5.70 (dt, J = 17 & 7 Hz, 1H), 5.30 (dd, J = 17 & 7 Hz, 1H), 3.64 (s, 3H), 1.15 (s, 3H), 0.91 (t, 3H); Ms: m/e 367.2732 (M^+). Calcd. for $C_{21}H_{37}O_4N$: 367.2720.

8. W. G. Salmond, M. A. Barta, and J. L. Havens, J. Org. Chem., 43, 790 (1978).

9. Personal communication with Dr. R. M. Scribner of this Department.

10. I am indebted to Drs. G. R. Christoph and W. F. Herblin of this Department for doing the biological tests. I would like to thank Dr R. M. Scribner for suggesting that compounds 3 and 4 could be worthwhile to prepare and kindly providing 2-methyl-1-hexene oxide.

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