CHEMISTRY LETTERS, pp. 1299-1300, 1979. Published by the Chemical Society of Japan

A STEREO AND REGIOSPECIFIC ROUTE TO THE SYNTHETIC INTERMEDIATE FOR THE SYNTHESIS OF 9(O)-METHANOPROSTACYCLIN

Masakatsu SHIBASAKI, Katsuhiko ISEKI[1], and Shiro IKEGAMI*
Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01

A stereo and regiospecific route to the synthetic intermediate, bicyclo[3.3.0]octan-2-one derivative, for the total synthesis of 9(O)-methanoprostacyclin is described starting from 1,3-cyclooctadiene, in which as a key reaction, the conjugate addition of the Gilman reagent to the bicyclo[3.3.0]oct-8-en-2-one skeleton is involved.

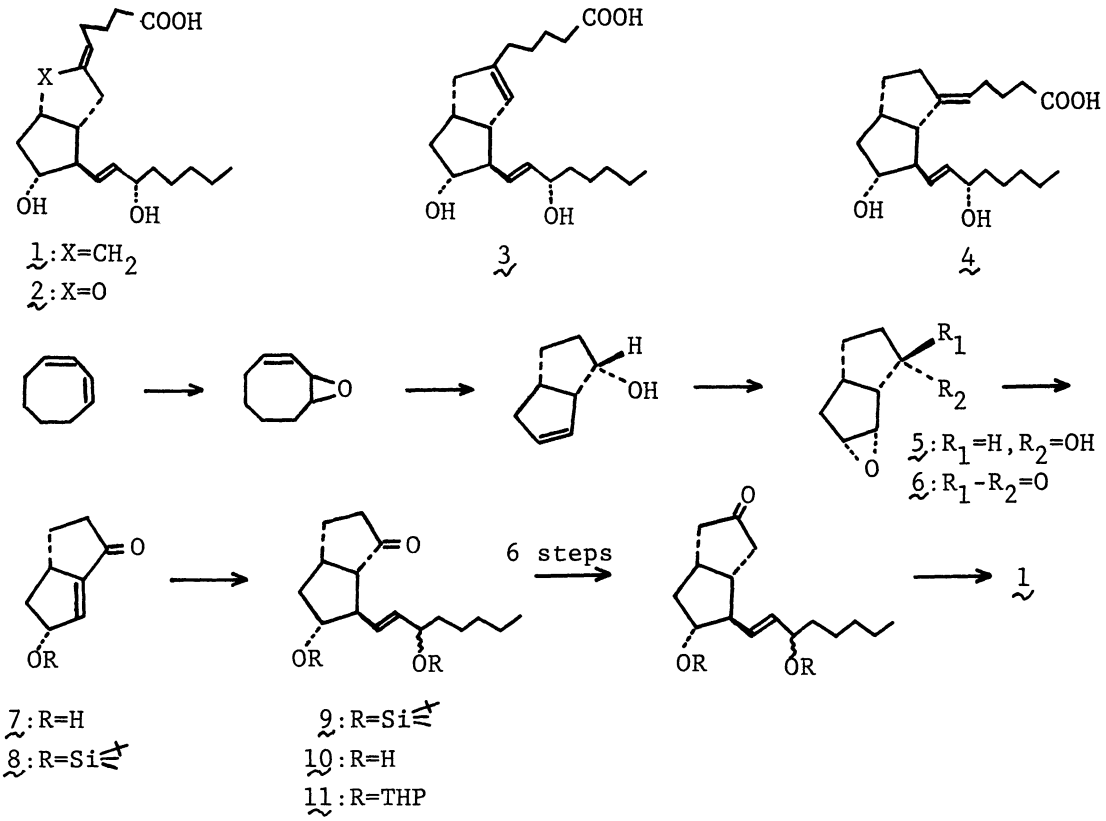
In the course of our synthetic studies directed toward 9(O)-methanoprostacyclin (1)[2], a highly stable and biologically potent analog of prostacyclin (2), the ketone (11) was demonstrated to be a key intermediate[2c] as shown in Scheme. Although previously the ketone (11) was successfully constructed from 1,3-cyclooctadiene in 10 steps, the synthesis suffered from unsatisfactory selectivity at the step of ω-side chain introduction. Because of the obvious need for an efficient route to 11, from which several other carbo-analogs (3 & 4) of prostacyclin should be obtained, the studies described herein were undertaken.

The *endo*-epoxide (5)[3], which can be synthesized stereospecifically from 1,3-cyclooctadiene in 3 steps[2c], was converted to the ketone (6), ir;ν_{max}^{film} 1740 cm-1, mass; 138 [M^+], with Collins reagent (8 equiv.) in methylene chloride at 0° for 1 h in nearly quantitative yield. Transformation of the ketone (6) to the α,β-unsaturated ketone (7) could be best achieved by treatment of 6 with sodium carbonate (10 equiv.) in water-*t*-butyl alcohol (3:1, 80ml/g) at room temperature for 4 h [7, ir;$\nu_{max}^{CHCl_3}$ 3610, 3450, 1708, 1641 cm-1, pmr;δ 6.32 (multiplet, 1H), mass; 138 [M^+], mp. 62-63°] in 50% yield based on the recovery of the starting ketone (6) (*ca.*25% recovery)[4].

Conjugate addition of the Gilman reagent to the *t*-butyldimethylsilyl derivative (8) obtained in the usual manner[5] is a very crucial step, since the attack at the carbonyl function might produce a 1,2-adduct[6].

After the successful observation of the conjugate addition using di-*n*-butylcopperlithium[7], reaction with the Gilman reagent derived from 3-(*t*-butyldimethylsilyloxy)-*trans*-1-octenyllithium[8] in ether at -78° was carried out and resulted in the formation of the desired ketone (9) [ir; ν_{max}^{film} 1740 cm-1, pmr;δ 5.45-5.27 (multiplet, 2H), mass; 494 [M^+] in 70% yield with a small amount of the 1,2-adduct. The stereochemistry of 9, which is another crucial element in the synthesis and expected from the previous result[9], was confirmed as follow: bis-*t*-butyldimethylsilyl derivative (9) was deprotected by treatment with a fluoride anion in tetrahydrofuran to afford the diol (10), which was identical with an authentic material[2c] obtained with unambiguous stereochemistry in all respects (ir, pmr, mass, tlc). Finally the diol (10) was converted to the intermediate (11) in the usual way[10].

Conclusively, the present new approach to 11 characterizes that the α-hydroxy group of bicyclo[3.3.0]oct-7-en-2-ol becomes a key functional moiety to introduce both groups of the 11-hydroxy and the ω-side chain stereo and regiospecifically. The synthetic intermediate (11) must be versatile in synthesis of prostacyclin analogs and is readily available by the present synthesis.



References and Notes

1) Visiting scientist from Research Laboratory, Mitsubishi Pharmaceutical Co. Ltd., Wakaguri, Ami-cho, Ibaragi 300-03.

2) a, K.Kojima and K.Sakai, Tetrahedron Lett., 1978, 3743; b, K.C.Nicolaou, W.S.Sipio, R.L. Magolda, S.Seitz, and W.E.Barnette, J. Chem. Soc., Chem. Commun., 1978, 1067; c, M.Shibasaki, J.Ueda, and S.Ikegami, Tetrahedron Lett., 1979, 433; d, A.Sugie, H.Shimomura, J.Katsube, and H.Yamamoto, *ibid.*, 1979, 2607.

3) The stereochemistry of the *endo*-epoxide (5) and its isomer was confirmed by NMR spectrometry using an Eu shift reagent ($Eu(fod)_3$).

4) With longer reaction time, serious decomposition of the product (7) was observed.

5) E.J.Corey and A.Venkateswarlu, J. Am. Chem. Soc., *94*, 6160 (1972).

6) G.H.Posner, Organic Reactions, *19*, 1 (1972). To our best knowledge, the conjugate addition of the Gilman reagent to the bicyclo[3.3.0]oct-8-en-2-one skeleton has never been reported.

7) The 1,4-adduct was obtained in good yield, while none of the 1,2-adduct was detected.

8) E.J.Corey and D.J.Beames, J. Am. Chem. Soc., *94*, 7210 (1972).

9) A.Mitra, " The Synthesis of Prostaglandin ", Wiley, New York, 1977, p.248.

10) Optically active 9(O)-methanoprostacyclin and related compounds would be obtained by the use of the optically active Gilman reagent.

(Received August 20, 1979)