PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Organometallics in Prostaglandin Synthesis [and Discussion]

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Organometallics in prostaglandin synthesis

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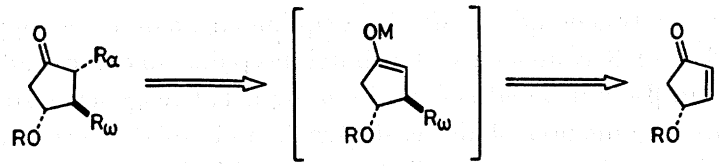
An extremely short way to prostaglandins has been opened by combining the newly devised organometallic methodologies. Convergent, one-pot creation of the prostanoid framework is achieved by organocopper conjugate addition of the *S*-configurated ω-side-chain unit to (*R*)-4-trialkylsiloxy-2-cyclopentenone followed by the organotin-aided trapping of the enolate intermediate by α-side-chain alkyl iodides. Prostaglandin E_2 can be prepared in only three steps from the chiral building units. The protected 5,6-didehydro-PGE_2 derivatives thus obtained serve as common intermediates for the synthesis of a variety of naturally occurring prostaglandins including prostacyclin. This approach is also useful for the controlled synthesis of isocarbacyclin.

Introduction

The role played by prostaglandins (PGs) in the human body is fascinating, and the oxygenated C_{20} carboxylic acids are now recognized as significant local hormones controlling a multitude of physiological processes. Development of an efficient chemical synthesis has been strongly desired, because organic synthesis is the only means to supply sufficient quantities of these important but naturally scarcely occurring substances and create the medicinally more cultivated artificial compounds. Organometallic chemistry provides powerful tools for synthesis of complex organic molecules and, as disclosed herein, use of the highly selective organometallic reagents and catalysts leads to efficient routes to natural and unnatural PGs.

We have pursued the realization of the convergent three-component coupling process, namely the simultaneous assembly of the five-membered cyclenone unit and two side chains, in view of its directness and flexibility (Noyori & Suzuki 1984). The ultimate goal along this line is, as illustrated by the retrosynthetic sequence (scheme 1), the one-pot construction of the whole PG framework via organometallic-aided conjugate addition of the eight-carbon ω-side-chain unit to 4-oxygenated 2-cyclopentenones followed by the trapping of the regiochemically defined enolate species by the seven-carbon halides having the α-side-chain structures.

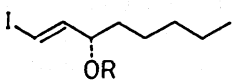


Scheme 1

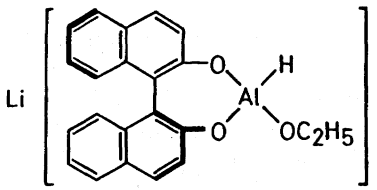
Access to the optically active building blocks

The requisite optically active building units are available in various ways. We have prepared the *S*-configurated ω-side-chain unit **1** by enantioselective reduction of the corresponding ketone with the (*S*)-BINAL-H reagent, **4** (Noyori *et al.* 1984*b*). The same hydride reagent also

allows enantioselective reduction of 4-cyclopentene-1,3-dione leading to (*R*)-4-hydroxy-2-cyclopentenone (**5**). The readily accessible racemic hydroxy ketone can be resolved by chromatography after condensation with the chiral hemiacylal **7** (Suzuki *et al.* 1982*b*, 1988*a*). The enantiomeric alcohols are also discriminatable kinetically by 1,3-hydrogen migration catalysed by the BINAP–Rh complex **8** (Kitamura *et al.* 1987). In addition, hydrogenation of the racemate with the BINAP–Ru complex **9** occurs with 11:1 enantiomer differentiation, providing a very convenient way to obtain homochiral silyl ether **6** (Kitamura *et al.* 1988).



1, R = H
2, R = $Si(CH_3)_2$-*t*-C_4H_9
3, R = THP



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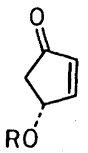
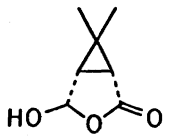


5, R = H
6, R = $Si(CH_3)_2$-*t*-C_4H_9



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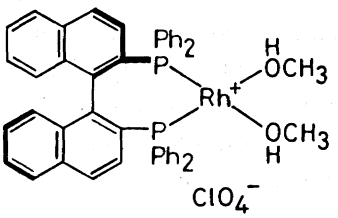

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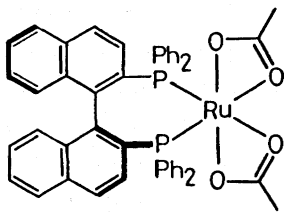

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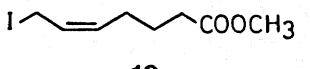
Three-component coupling synthesis

Organocopper reagents generated *in situ* from equimolar amounts of copper(I) iodide and organolithium and 2 to 3 equivalents of tributylphosphine undergo high-yield conjugate addition to various α, β-unsaturated ketones by using a 1:1 reagent:substrate ratio (Suzuki *et al.* 1984*a*). Thus introduction of the ω-side-chain unit to the five-membered ring was accomplished by this stoichiometry-controlled reaction with the homochiral cyclopentenone **6** and the phosphine-complexed organocopper reagent formed from the vinylic iodide **2**, securing the *trans* C-11/C-12 relation (PG numbering). The alkylative trapping of the regio-defined intermediate was realized by utilization of organotin transmetalation technique (Suzuki *et al.* 1985, 1988*b*). Thus sequential treatment of the organocopper reagent with the enone **6**, HMPA, triphenyltin chloride, and the *Z*-allylic iodide **10** afforded the desired product **12** in

high yield. Removal of the silyl protective groups followed by enzymatic hydrolysis of the resulting **14** completes the synthesis of PGE_2 (**15**). As such the device of the tandem conjugate addition/alkylation sequence has opened a simple, three-step route to PGE_2. Synthesis of PG_s of the D series requires the reversal of the oxidation states at C-9 and C-11. The rectification of such functionalities is readily achievable by choosing appropriate protective groups in the starting chiral alcohol units. The vicinal carba-condensation of the siloxy cyclopentenone **6** with the THP-protected ω-side-chain precursor **3** and alkylating agent **10** afforded the prostanoid skeleton **13**, which is convertible to PGD_2 (**18**) by the six-step sequence: (i) stereoselective (100%) reduction of the 9-keto group with L-Selectride, (ii) THP protection of the alcohol, (iii) desilylation, (iv) saponification of the methyl ester, (v) Jones oxidation of the 9-hydroxyl, and (vi) removal of the THP protection (Suzuki *et al.* 1984*b*).



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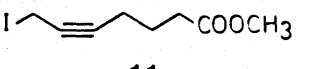

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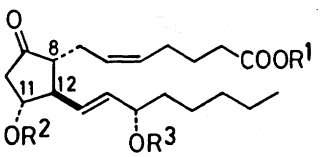
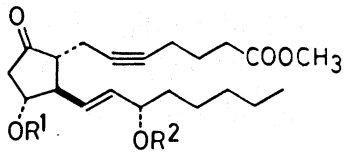


12, $R^1 = CH_3$; $R^2 = R^3 = Si(CH_3)_2\text{-}t\text{-}C_4H_9$

13, $R^1 = CH_3$; $R^2 = Si(CH_3)_2\text{-}t\text{-}C_4H_9$; R^3 = THP

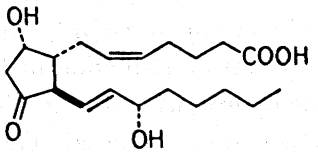
14, $R^1 = CH_3$; $R^2 = R^3 = H$

15, $R^1 = R^2 = R^3 = H$



16, $R^1 = R^2 = Si(CH_3)_2\text{-}t\text{-}C_4H_9$

17, $R^1 = Si(CH_3)_2\text{-}t\text{-}C_4H_9$; R^2 = THP



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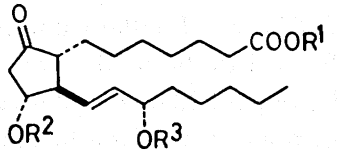
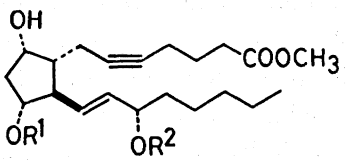


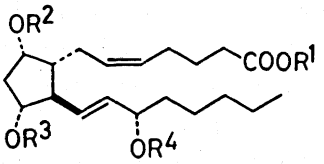
19, $R^1 = CH_3$; $R^2 = R^3 = Si(CH_3)_2\text{-}t\text{-}C_4H_9$

20, $R^1 = R^2 = R^3 = H$

Placement of an acetylenic bond at the C-5–C-6 positions allows for a general synthesis of naturally occurring PGs (Suzuki *et al.* 1982*a*, 1985 1988*b*). When the one-pot, three-component coupling was conducted with **2**, **6**, and the propargylic iodide **11**, the 5,6-didehydro-PGE_2 derivative **16** was produced. The controlled hydrogenation of the triple bond, leading to PGs of 1 and 2 series, and the stereoselective reduction of the 9-keto group giving the 9α-alcohol, if necessary, result in a variety of PGs. Partial hydrogenation of the acetylenic

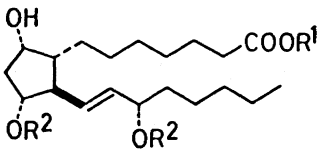


21, $R^1 = R^2 =$ $Si(CH_3)_2$-t-C_4H_9



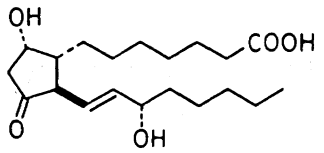
22, $R^1 = CH_3$; $R^2 = H$; $R^3 = R^4 =$ $Si(CH_3)_2$-t-C_4H_9

23, $R^1 = R^2 = R^3 = R^4 = H$



24, $R^1 = CH_3$; $R^2 =$ $Si(CH_3)_2$-t-C_4H_9

25, $R^1 = R^2 = H$



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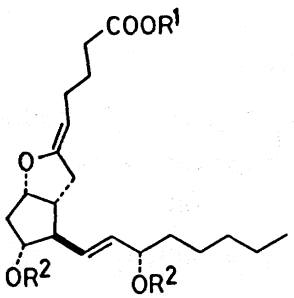
bond in the common intermediate **16**, giving the *Z*-double bond, was accomplished over 5% $Pd/BaSO_4$ catalyst to afford **12**; whereas the controlled hydrogenation over Pd/C produced **19**, leaving the C-13–C-14 double bond intact. The desilylation and enzymatic hydrolysis gave PGE_1 (**20**).

Reduction of **16** with L-Selectride gave the 9α-alcohol **21** exclusively. Notably, although the (*S*)-BINAL-H reagent (Noyori *et al.* 1984*a*) was almost inert to the ketone **16**, the reduction with the *R*-enantiomer proceeded smoothly to form the 9α-alcohol **21** with a sufficiently high stereoselectivity ($9\alpha/9\beta \approx 99:1$). The chiral disposition of the ring substituents appears to play a particular role in such unprecedented high kinetic discrimination ($k_R/k_S > 130$!). Hydrogenation of **21** over Lindlar catalyst gave **22**, whereas the use of 5% $Pd/BaSO_4$ catalyst afforded **24**, identical to the product obtained by L-Selectride reduction of **19**. Deprotection of the hydroxyl groups of **22** or **24** followed by alkaline hydrolysis of the ester led to $PGF_{2\alpha}$ (**23**) and $PGF_{1\alpha}$ (**25**), respectively. In a like manner, PGDs can be prepared. The organometallic mediated union of **3**, **6**, and **11** afforded the acetylenic ketone **17**. L-Selectride reduction of the 9-keto function, partial hydrogenation of the acetylenic linkage over the Lindlar or Pd/C catalyst, and subsequent functional group transposition afforded PGD_2 (**18**) or PGD_1 (**26**).

Synthesis of prostacyclin

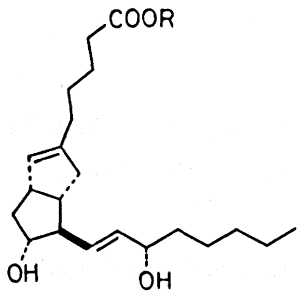
The acetylenic alcohol **21** can be transformed to prostacyclin (PGI_2, **28**) by a mild intramolecular alkoxypalladation/depalladation procedure. Thus cyclization of **21** with $PdCl_2(C_6H_5CN)_2$ in THF at low temperature followed by depalladation with ammonium formate afforded the desired **27** with excellent stereoselectivity, $5Z/5E > 33:1$. It is clear that the alkoxypalladation to the C-5–C-6 triple bond is occuring in an anti 5-*exo-dig* fashion and

that the reductive depalladation is accomplished with retention of the alkenyl ether stereointegrity. This cyclization procedure is superior to the alkoxymercuration/demercuration method (Suzuki *et al* 1983). Deblocking of the hydroxyl groups of **27** followed by alkaline hydrolysis of the ester produced PGI_2 (**28**).



27, $R^1 = CH_3$; $R^2 = Si(CH_3)_2\text{-}t\text{-}C_4H_9$

28, $R^1 = R^2 = H$

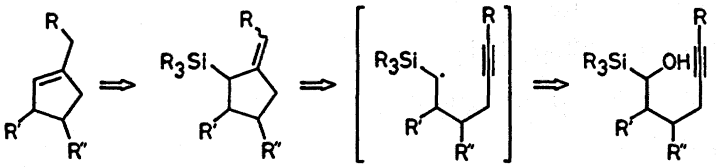


29, R = H

30, $R = CH_3$

Controlled synthesis of isocarbacyclin

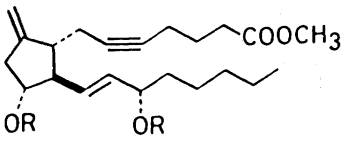
Natural prostacyclin (**28**) possesses remarkable antihypertensive and platelet aggregation-inhibiting properties, but the sensitivity of the 2-alkylidenetetrahydrofuran structure to hydrolytic destruction must be overcome in order to be a clinically useful agent. Isocarbacyclin (**29**), among the various carbocyclic analogues so far prepared, has received particular attention as a promising therapeutic agent for cardiovascular and circulatory diseases because of its potent physiological activities and satisfactory chemical stability (Shibasaki *et al.* 1983). Efficient synthesis of **29** requires a controlled construction of the bicyclo[3.3.0]octene framework and our basic strategy for the regio-defined introduction of the double bond to the fused five-membered ring is outlined by the retrosynthetic sequence (scheme 2). This radical chemistry coupled with the above described three-component coupling PG synthesis has opened an efficient route to **29** (Suzuki *et al.* 1987).



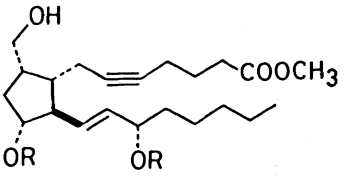
Scheme 2

First, the 9-keto group of **16** was methylenated by a $Zn\text{–}CH_2Br_2\text{–}TiCl_4$ mixed reagent to give **31**. Stereoselective hydroboration of **31** with 9-borabicyclo[3.3.1]nonane followed by workup with alkaline hydrogen peroxide gave the hydroxymethyl derivative **32**. Oxidation of the primary alcohol with pyridinium dichromate, giving the labile aldehyde **33**, followed by immediate silylation with dilithium cyanobis(dimethylphenylsilyl)cuprate afforded the

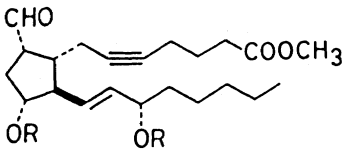
requisite α-silylated alcohol **34**. The key cyclization to the bicyclo[3.3.0]octane framework was cleanly effected by the Barton's organotin chemistry. Thus reaction of the xanthate **35** with excess tributylin hydride in the presence of di-*tert*-butyl peroxide led to **36**. Deblocking of the 11- and 15-hydroxyls of **36** and subsequent protodesilylation of **37** completed the synthesis of **30**. Alkaline hydrolysis of the methyl ester gave **29**.



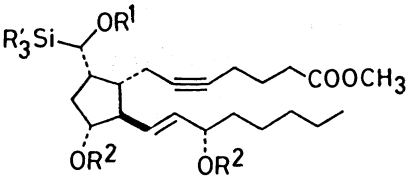
31, R = $Si(CH_3)_2$-*t*-C_4H_9



32, R = $Si(CH_3)_2$-*t*-C_4H_9



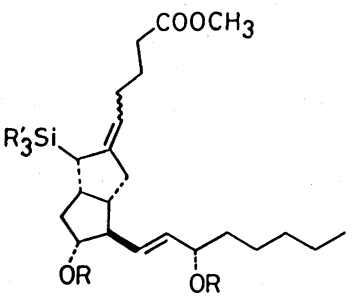
33, R = $Si(CH_3)_2$-*t*-C_4H_9



SiR'_3 = $Si(CH_3)_2C_6H_5$

34, R^1 = H; R^2 = $Si(CH_3)_2$-*t*-C_4H_9

35, R^1 = $C(S)SCH_3$; R^2 = $Si(CH_3)_2$-*t*-C_4H_9



SiR'_3 = $Si(CH_3)_2C_6H_5$

36, R = $Si(CH_3)_2$-*t*-C_4H_9

37, R = H

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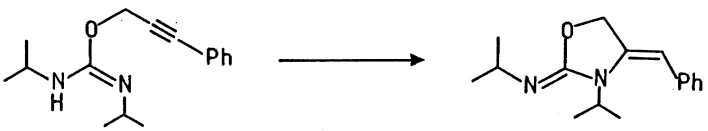
Discussion

B. T. Golding (*Department of Organic Chemistry, University of Newcastle upon Tyne, U.K.*). Did Professor Noyori try Ag^{+} catalysis for the cyclization of acetylenic alcohols? We have recently found (S.P. Collingwood & B. T. Golding, unpublished results) that cyclizations of the kind shown in scheme D1 proceed well under catalysis by silver trifluoromethanesulphonate ($Ag^{I} > Cu^{I}$, Cu^{II} or Pd^{II}).



Scheme D1

R. Noyori. I have not tried the Ag^{+} catalysis. Our Pd^{II}-aided cyclization proceeded nicely in a stereo-defined manner without concomitant double-bond migration. However, we need a stoichiometric amount of the Pd^{II} complex. We should try the catalytic method. I thank Professor Golding for his suggestion.

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