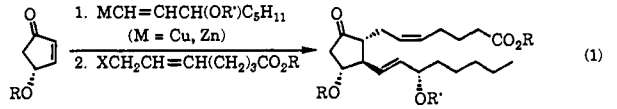
Organopalladium Approaches to Prostaglandins. 11. Synthesis of $PGF_{2\alpha}$ and 12-*epi*-$PGF_{2\alpha}$ by the Controlled, One-Step, Palladium-Promoted, Intermolecular Coupling of Three Different Alkenes‡

Richard C. Larock* and Nam Ho Lee

Department of Chemistry, Iowa State University
Ames, Iowa 50011

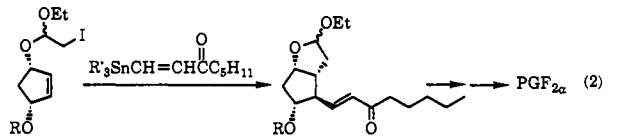
Received May 13, 1991

The synthesis of prostaglandins has recently received considerable attention.[1] Among the most efficient approaches to the primary prostaglandins has been the three-component coupling[2] of organocopper reagents, organic halides, and enones or derivatives[3] (eq 1). Tandem radical cyclization[4] has afforded another



(1)

efficient route to these physiologically important compounds (eq 2).[5] Recent interest in the efficient synthesis of the primary

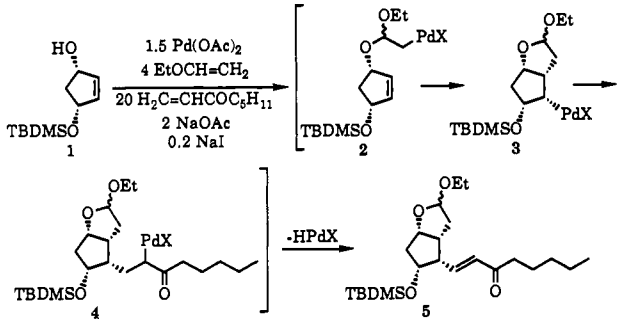


(2)

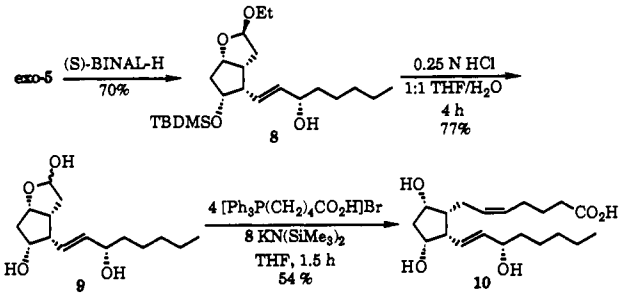
prostaglandins via organopalladium intermediates[6] prompts us to report a novel new approach to prostaglandins which nicely complements these earlier approaches.

The key starting material in our synthesis of $PGF_{2\alpha}$ and 12-*epi*-$PGF_{2\alpha}$ is the readily available chiral alcohol *cis*-4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopenten-1-ol (**1**).[5] The one-step intermolecular coupling of three different alkenes, **1**, ethyl vinyl ether, and 1-octen-3-one, in the presence of $Pd(OAc)_2$, NaOAc, and a catalytic amount of NaI (no solvent) at room temperature for 3 h affords the key bicyclic enone **5** ($[\alpha]^{22}_D = -51.1°$) as a 2–3:1 mixture of exo and endo isomers, respectively, in 72% yield (Scheme I). This extraordinary one-pot transformation undoubtedly involves sequential (1) oxypalladation of the electron-rich vinyl ether[7] to produce **2**, (2) intramolecular cis insertion of the cyclopentene[7b] to afford intermediate **3**, which is blocked from syn palladium β-hydride elimination by the silyloxy group, (3) carbopalladation of the electron-poor enone, and finally (4) palladium β-hydride elimination to produce the desired product **5**.[8] Since the exo and endo isomers are easily separated or the endo isomer can be cleanly epimerized in 98% yield to the exo isomer upon treatment with 0.3 equiv of pyridinium *p*-toluenesulfonate in EtOH for 1 day at room temperature, all subsequent work has been carried out on pure *exo*-**5**.

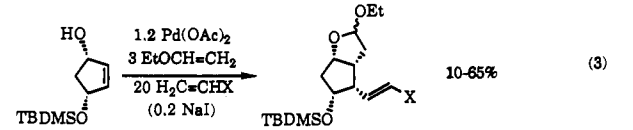
Scheme I



Scheme II



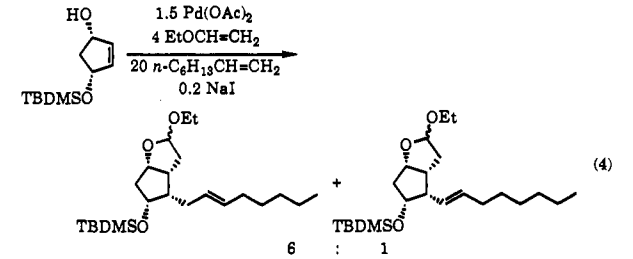
This unique multiinsertion process affords easy entry into a variety of analogues of this highly hindered bicyclic system, although no attempt has been made to optimize the yields (eq 3).



(3)

X = COEt, COMe, CO_2Me, CHO, Ph, SO_2Ph, CMe_2OH, $CH(OAc)C_5H_{11}$

The use of 1-octene in this reaction resulted in the formation of a mixture of isomeric alkenes in 54% yield (eq 4). This chemistry



(4)

appears particularly promising for the synthesis of naturally occurring *cis*-2-(2-alkenyl)-3-alkylcyclopentanones, such as 12-oxophytodienoic acid,[9] (−)-preclavulone A,[10] and (+)-methyl epijasmonate.[11]

‡ Dedicated to Professor George Zweifel on his retirement.

(1) (a) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic Press: New York, 1977. (b) Mitra, A. *The Synthesis of Prostaglandins*; John Wiley and Sons: New York, 1977. (c) *New Synthetic Routes to Prostaglandins and Thromboxanes*; Roberts, S. M., Scheinmann, F., Eds.; Academic Press: New York, 1982.

(2) (a) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847. (b) Noyori, R. *Chem. Br.* **1989**, *25*, 883.

(3) (a) Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 5563. (b) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348. (c) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1986**, *108*, 5655. (d) Tanaka, T.; Okamura, N.; Bannai, K.; Hazato, A.; Sugiura, S.; Tomimori, K.; Manabe, K.; Kurozumi, S. *Tetrahedron* **1986**, *42*, 6747. (e) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641. (f) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718. (g) Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.

(4) Curran, D. P. In *Advances in Free Radical Chemistry*; Tanner, D., Ed.; JAI Press: Greenwich, 1990; pp 121–157.

(5) (a) Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384. (b) Keck, G. E.; Burnett, D. A. *J. Org. Chem.* **1987**, *52*, 2958.

(6) (a) Larock, R. C.; Kondo, F.; Narayanan, K.; Sydnes, L. K.; Hsu, M. H. *Tetrahedron Lett.* **1989**, *30*, 5737. (b) Torii, S.; Okumoto, H.; Akahoshi, F.; Kotani, T. *J. Am. Chem. Soc.* **1989**, *111*, 8932.

(7) (a) Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 809. (b) Larock, R. C.; Stinn, D. E. *Tetrahedron Lett.* **1989**, *30*, 2767. (c) Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2050.

(8) For the palladium-promoted, *intramolecular* sequential insertion of alkenes, see: (a) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 701. (b) Grigg, R.; Dorrity, M. J.; Malone, J. F.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1990**, *31*, 1343. (c) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846. (d) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328. (e) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454.

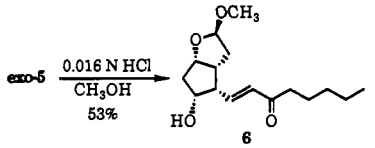
(9) (a) Crombie, L.; Mistry, K. M. *J. Chem. Soc., Chem. Commun.* **1988**, 537. (b) Grieco, P. A.; Abood, N. *J. Org. Chem.* **1989**, *54*, 6008.

(10) Corey, E. J.; Xiang, Y. B. *Tetrahedron Lett.* **1988**, *29*, 995.

(11) (a) Acree, T. E.; Nishida, R.; Fukami, H. *J. Agric. Food Chem.* **1985**, *33*, 425. (b) Seto, H.; Yoshioka, H. *Chem. Lett.* **1990**, 1797.

0002-7863/91/1513-7815$02.50/0

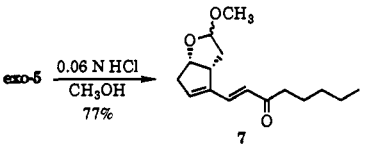
Enone **5** is readily converted to the isomerically pure *exo*-methoxy alcohol **6** upon treatment with 0.016 N HCl in methanol for 3 days at room temperature (eq 5). Since this alcohol has



(5)

been prepared previously by a biosynthetic approach[12] and subsequently epimerized to the corresponding β-enone, which has been carried on to $PGF_{2\alpha}$ in three routine subsequent steps, this synthesis constitutes one of the more efficient chiral approaches to $PGF_{2\alpha}$.

Enone **5** is also readily converted to a mixture of diastereomeric dienones **7** in 77% yield when treated with HCl in methanol for 3 days (eq 6). Enone **6** also gives dienone **7** in over 90% yield



(6)

when treated with 75 and 25 equiv of acetic acid and morpholine, respectively, in 2:1 DME/H_2O for 72 h at 70 °C. Dienone **7** should prove particularly valuable in the synthesis of the C prostaglandins.[13]

Since 12-*epi*-$PGF_{2\alpha}$ (**10**) has previously only been synthesized by a rather tedious process[14] or via a side product arising during the synthesis of $PGF_{2\alpha}$,[15] and apparently nothing is known about its pharmacological properties, we elected to complete its synthesis using readily available enone **5** (Scheme II). Reduction with (*S*)-BINAL-H[16] affords a single product assigned structure **8** in analogy with previous such reductions. Hydrolysis proceeded in 77% yield. The attempted Wittig reaction using sodium dimsyl[17] or KO-*t*-Bu[18] to generate the ylide proved unsuccessful. However, the use of potassium hexamethyldisilazide[10] afforded 12-*epi*-$PGF_{2\alpha}$ (**10**) in 54% yield. Unfortunately, 12-*epi*-$PGF_{2\alpha}$ exhibited limited activity toward blood platelet aggregation ($I_{50} > 1000$ μM against ADP-induced aggregation and $I_{50} = 179$ μM against arachidonic acid induced aggregation).

In conclusion, the controlled, palladium-promoted, one-step, intermolecular insertion of three different alkenes affords a highly efficient synthesis of compound **5**, a valuable intermediate in the formal synthesis of $PGF_{2\alpha}$. This same intermediate affords 12-*epi*-$PGF_{2\alpha}$ in only four steps and 21% overall yield from the readily available chiral starting material **1**.

Acknowledgment. We gratefully acknowledge the National Institutes of Health and the American Heart Association—Iowa Affiliate for financial support; Bristol-Myers Squibb for biological testing; and Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., Ltd., for the palladium acetate.

Supplementary Material Available: Procedures for the synthesis of compounds **5–9** and appropriate spectral data (6 pages). Ordering information is given on any current masthead page.

(12) Corey, E. J.; Shimoji, K.; Shih, C. *J. Am. Chem. Soc.* **1984**, *106*, 6425.
(13) (a) Corey, E. J.; Moinet, G. *J. Am. Chem. Soc.* **1973**, *95*, 7185. (b) Schwarz, S.; Weber, G.; Depner, J.; Schaumann, J.; Schick, H.; Welzel, H. P. *Tetrahedron* **1982**, *38*, 1261.
(14) Brown, E. D. Ger. Offen. DE 2,360,893, 12 June 1973; *Chem. Abstr.* **1974**, *81*, 120096e.
(15) Brewster, D.; Meyers, M.; Ormerod, J.; Otter, P.; Smith, A. C. B.; Spinner, M. E.; Turner, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2796.
(16) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.
(17) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.
(18) Howard, C. C.; Newton, R. F.; Reynolds, D. P.; Wadsworth, A. H.; Kelly, D. R.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 852.

A Complete Change of Stereoselectivity in Sialic Acid Aldolase Reactions: A Novel Synthetic Route to the KDO Type of Nine-Carbon L Sugars[1]

Christine Gautheron-Le Narvor, Yoshitaka Ichikawa, and Chi-Huey Wong*

Department of Chemistry, The Scripps Research Institute
10666 North Torrey Pines Road
La Jolla, California 92037
Received April 26, 1991

A major synthetic value of enzyme catalysis is its predictable stereoselectivity.[2] A change of stereoselectivity, though very unusual, may occur, however, with different substrate structures,[3] temperatures,[4] or solvents.[5] These selectivity changes are often not very significant, with some exceptions[3] where the enantioselectivity is inverted. In the case of enzymatic aldol reactions, the diastereofacial selectivity for the aldehyde component is often consistent and completely controlled by the enzyme as documented by numerous reactions catalyzed by fructose-1,6-diphosphate aldolase[6] and *N*-acetylneuraminic acid (or sialic acid) aldolase[7] (EC 4.1.3.3). We report here a complete reversal of stereoselectivity in the sialic acid aldolase catalyzed reactions of pyruvate with L-mannose and with 6-deoxy-L-mannose (L-rhamnose) (Scheme I).

NeuAc aldolase is a type I aldolase forming an enamine intermediate with pyruvate, which reversibly reacts with the second substrate *N*-acetylmannosamine to give NeuAc.[8] The enzyme accepts many aldoses as acceptor substrates. In all reactions, the enamine intermediate approaches the *si* face of the incoming aldehyde substrate to form a new stereogenic center of *S* configuration.[7] In the reaction with L-mannose or 6-deoxy-L-mannose (L-rhamnose), however, a single product with a new stereogenic center of *R* configuration generated via *re* face attack was obtained in each case in >80% yield. Both products adopt a $^5C_2$ conformation as indicated by the adjacent transaxial coupling of protons at positions 3, 4, and 5. The enzyme products have the same NMR

(1) Supported by the NIH (GM 44154).
(2) For reviews: Whitesides, G. M.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 617. Jones, J. B. *Tetrahedron* **1986**, *42*, 3351. Yamada, H.; Shimizu, S. *Angew. Chem., Int. Ed. Engl.* **1988**, 27, 622. Wong, C.-H. *Science* **1989**, *244*, 1145. Ohno, M.; Otsuka, M. *Org. React. (N.Y.)* **1989**, *37*, 1. Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695.
(3) Mohr, P.; Waespe-Sarcevic, N.; Tamn, C.; Gawronska, K.; Gawronski, J. K. *Helv. Chim. Acta* **1983**, *66*, 2501. Sabbioni, G.; Shea, M. L.; Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1984**, 236. Ohno, M.; Kobayashi, S.; Iimori, T.; Wang, Y.-F.; Izawa, T. *J. Am. Chem. Soc.* **1981**, *103*, 2405. Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 3127. Lalonde, J. J.; Bergbreiter, D. E.; Izawa, T. *J. Am. Chem. Soc.* **1981**, *103*, 2405. Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 2323.
(4) Pham, V. T.; Phillips, R. S.; Ljungdahl, L. G. *J. Am. Chem. Soc.* **1989**, *111*, 1935. Keinan, E.; Hafeli, E. K.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 162.
(5) Sakurai, T.; Morgolin, A. L.; Russell, A. J.; Klibanov, A. M. *J. Am. Chem. Soc.* **1988**, *110*, 7236. Fitzpatrick, P. A.; Klibanov, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 3166.
(6) In most cases, the "D" isomer of an α-substituted aldehyde reacts faster than the L isomer, both with *si*-facial selectivity. The Cram-Felkin mode[9] of attack on the "D" aldehyde is therefore proposed for the transition state. Toone, E. J.; Simon, E. S.; Bednarski, M. D.; Whitesides, G. M. *Tetrahedron* **1989**, *45*, 5365. Bednarski, M. D.; Simon, E. S.; Bischefberger, N.; Tessner, W. D.; Kim, M. J.; Lees, W.; Saito, T.; Waldmann, H.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 627. Straub, A.; Effenberger, F.; Fischer, P. *J. Org. Chem.* **1990**, *55*, 3926. Durrwachter, J. R.; Drueckhammer, D. G.; Nozaki, K.; Sweers, H. M.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 4175. von der Osten, C. H.; Sinskey, A. J.; Barbas, C. F., III; Pederson, R. L.; Wang, Y.-F.; Wong, C.-H. *J. Am. Chem. Soc.* **1989**, *111*, 3924. Kajimoto, T.; Liu, K. K.-C.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Porco, A. J., Jr.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6187.
(7) Anti-Cram-Felkin attack is generally observed for good chiral aldehyde substrates, and Cram-Felkin attack is observed for weak substrates. In both cases, a *si*-facial selectivity was observed. (a) Auge, C.; David, S.; Gautheron, C.; Malleron, A.; Cavaye, B. *New J. Chem.* **1988**, *12*, 733. (b) Auge, C.; Gautheron, C.; David, S.; Malleron, A.; Cavaye, B.; Bouxom, B. *Tetrahedron* **1990**, *46*, 201. (c) Drueckhammer, D. G.; Hennen, W. J.; Pederson, R. L.; Barbas, C. F., III; Gautheron, C. M.; Krach, T.; Wong, C.-H. *Synthesis* **1991**, *7*, 499. A loss of diastereoselectivity was observed with D-arabinose as a substrate (see ref 7c).
(8) Deijl, C. M.; Vliegenthart, F. G. *Biochem. Biophys. Res. Commun.* **1983**, *111*, 668. Shukla, A. K.; Schauer, R. *Anal. Biochem.* **1986**, *158*, 158.

0002-7863/91/1513-7816$02.50/0