ORGANIC LETTERS

2009
Vol. 11, No. 14
3104−3107

Synthesis of Prostaglandin and Phytoprostane B$_1$ Via Regioselective Intermolecular Pauson−Khand Reactions†

Ana Vázquez-Romero, Lydia Cárdenas, Emma Blasi, Xavier Verdaguer,* and Antoni Riera*

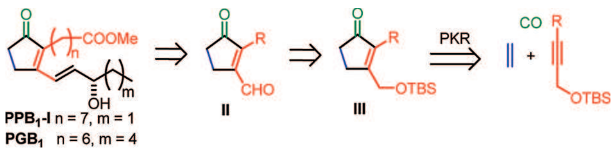
Unitat de Recerca en Síntesi Asimètrica (URSA-PCB), Institute for Research in Biomedicine (IRB Barcelona) and Departament de Química Orgànica, Universitat de Barcelona, Parc Científic de Barcelona c/ Baldiri Reixac 10, 08028 Barcelona, Spain

antoni.riera@irbbarcelona.org; xavier.verdaguer@irbabarcelona.org

Received June 2, 2009

Downloaded by UNIV OF BARCELONA on July 9, 2009
Published on June 22, 2009 on http://pubs.acs.org | doi: 10.1021/ol901213d

ABSTRACT



A new approach to the synthesis of prostaglandin and phytoprostanes B$_1$ is described. The key step is an intermolecular Pauson−Khand reaction between a silyl-protected propargyl acetylene and ethylene. This reaction, promoted by NMO in the presence of 4 Å molecular sieves, afforded the 3-*tert*-butyldimethylsilyloxymethyl-2-substituted-cyclopent-2-en-1-ones (III) in good yield and with complete regioselectivity. Deprotection of the silyl ether, followed by Swern oxidation, gave 3-formyl-2-substituted-cyclopent-2-en-1-ones (II). Julia olefination of the aldehydes II with the suitable chiral sulfone enabled preparation of PPB$_1$ type I and PGB$_1$.

Prostaglandins are hormone-like compounds found in virtually all tissues and organs.[1] Mammalian prostaglandins and their isomers, isoprostanes,[2] have a 20-carbon skeleton, as they derive metabolically from arachidonic acid. All compounds feature a five-membered hydrocarbon ring of various oxidative degrees as well as two side chains of different lengths and functionalization. Prostaglandins perform a myriad of biological activities and are implicated in many diseases.[3] Some naturally occurring prostaglandins, such as prostaglandin E$_2$ (PGE$_2$, dinoprostone), and several synthetic analogues are important drugs.[4] Prostaglandin B$_1$ (PGB$_1$), which contains a cyclopentenone ring and whose two side chains are attached directly to the double bond of this ring, is formed by nonenzymatic dehydration of PGE$_1$. PGB$_1$ has shown remarkable affinity for peroxisome proliferator-activated receptor-γ (PPAR-γ), which is involved in fat deposition and metabolism, and its oligomers exhibit antioxidant and ionophoric activity.[5] Phytoprostanes are botanical analogues of prostaglandins.[6] In higher plants, the main polyunsaturated fatty acid is α-linolenic acid. Therefore, most

† Dedicated to Prof. Josep Font on the occasion of his 70th birthday.

(1) (a) *Prostaglandins, Leukotrienes and other Eicosanoids*; Marks, F.; Fürstenberger, G., Eds.; Wiley-VCHG: Weinheim, 1999. (b) Rokach, J.; Khanapure, S. P.; Hwang, S.-W.; Adiyaman, M.; Lawson, J. A.; FitzGerald, G. A. *Prostaglandins* **1997**, *54*, 823.

(2) (a) Roberts, L. J.; Milne, G. L. *J. Lipid Res.* **2009**, S219. (b) Durand, T.; Cracowski, J.; Berdeaux, O. *Pathol. Biol.* **2005**, *53*, 349. (c) Rokach, J.; Kim, S.; Bellone, S.; Lawson, J. A.; Pratico, D.; Powell, W. S.; FitzGerald, G. A. *Chem. Phys. Lipids* **2004**, *128*, 35. (d) Milne, G.; Musiek, E.; Morrow, J. *Biomarkers* **2005**, *10*, S10.

(3) (a) Jahn, U.; Galano, J.; Durand, T. *Angew.Chem., Int.Ed.* **2008**, *47*, 5894.

(4) (a) Backlund, M. G.; Mann, J. R.; DuBois, R. N. *Oncology* **2005**, *69*, 28. (b) Cimino, P. J.; Keene, C. D.; Breyer, R. M.; Montine, K. S.; Montine, T. J. *Curr. Med. Chem.* **2008**, *15*, 1863. (c) Logan, C. M.; Giordano, A.; Puca, A.; Cassone, M. *Cancer Biol. Ther.* **2007**, *6*, 1517. (d) Sugimoto, Y.; Narumiya, S. *J. Biol. Chem.* **2007**, *282*, 11613.

(5) (a) Franson, R. C.; Rosenthal, M. D. *Biochim. Biophys. Acta, Lipids Lipid Metab.* **1989**, *1006*, 272. (b) Uribe, S.; Villalobos-Molina, R.; Devlin, T. M. *Biochem. Biophys. Res. Commun.* **1987**, *143*, 1024. (c) DeTitta, G. T. *Science* **1976**, *191*, 1271.

(6) Mueller, M. J. *Curr. Opin. Plant Biol.* **2004**, *7*, 441.

10.1021/ol901213d CCC: $40.75 © 2009 American Chemical Society
Published on Web 06/22/2009