ORGANIC LETTERS

2009
Vol. 11, No. 14
3104−3107

Synthesis of Prostaglandin and Phytoprostane B_1 Via Regioselective Intermolecular Pauson−Khand Reactions†

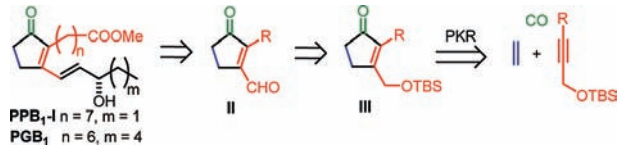
Ana Vázquez-Romero, Lydia Cárdenas, Emma Blasi, Xavier Verdaguer,* and Antoni Riera*

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

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
Published on Web 06/22/2009

phytoprostanes are 18-carbon compounds and chiefly differ from prostaglandins in the lengths of their side chains. There are several classes of phytoprostanes, and their levels increase under conditions of enhanced free-radical generation.[7] Moreover, due to their structural similarity to isoprostanes, phytoprostanes can interfere with these at the receptor level.[8] To date, different series of phytoprostanes are known (E, B, A, and J): PPB_1 type I and PPB_1 type II, both of which show interesting biological properties[9] (Figure 1).

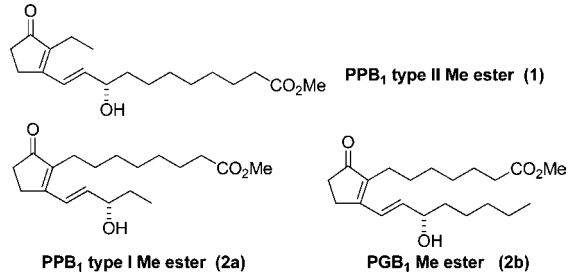


Figure 1. Structures of the methyl esters of prostanes B_1: PGB_1, PPB_1 type I, and PPB_1 type II.

The biological importance of prostanes and the challenges inherent to their synthesis have stimulated research on efficient, stereoselective chemistry for their preparation.[10,11] The disubstituted cyclopentenone common to prostaglandin B_1 and phytoprostanes B_1 suggests that these compounds could be obtained via intermolecular Pauson−Khand reaction between an internal alkyne and ethylene. Although Pauson−Khand chemistry is now widely used for five-membered hydrocarbon cycles,[12] the intermolecular version using internal alkynes has scarcely been used, probably because of the lower reactivity of these alkynes (compared to the terminal ones) as well as the difficulty of regioselective control.

Herein we describe a straightforward, regio- and stereoselective route to prostaglandin B_1 and phytoprostanes B_1 (Figure 1) which is based on intermolecular Pauson−Khand reaction of internal alkynes.

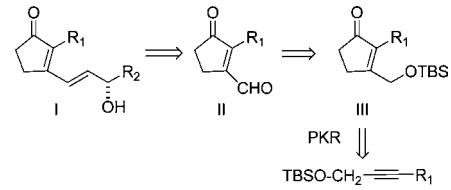


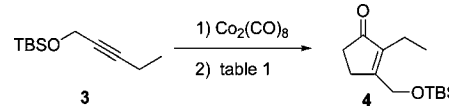
Figure 2. General retrosynthetic analysis of prostanes B_1.

Our approach is outlined in Figure 2. We envisaged synthesizing prostanes B_1 (Figure 2, compounds **I**) by olefination of the aldehydes **II** with suitable chiral hydroxy-alkyl fragments. We expected that **II** could be readily obtained from the protected hydroxymethylcyclopentenones **III**, which would be obtained by Pauson−Khand reaction of ethylene and the appropriate internal acetylene.

The underlying challenge was regiochemical control of the reaction since the two sides of the acetylene are fairly similar. In Pauson−Khand reactions of acetylenes in which the steric hindrance for each substituent is similar, Greene and Gimbert[13] showed that regioselectivity is mostly influenced by the difference in electronegativity between both substituents. In these cases, the most electron-withdrawing group usually goes to the β position. We reasoned that, although low, the electronegativity of a silyloxymethyl group could be sufficient to enable control over regioselectivity. Thus, we planned to synthesize **III** by Pauson−Khand reaction of acetylenes containing an aliphatic chain and a hydroxymethyl group protected as *tert*-butyldimethylsilyl ether.

To optimize the conditions, we chose the alkyne **3** as a precursor to phytoprostane PPB_1 type II. Commercially available pent-3-yn-1-ol was protected as the *tert*-butyldimethylsilyl ether under standard conditions (91% yield) and subsequently treated with octacarbonyl dicobalt in hexanes. After concentration in vacuo, the cobalt complex was submitted to several Pauson−Khand conditions (see Table 1). The standard thermal conditions under

Table 1. Pauson−Khand Synthesis of the Cyclopentenone **4** Using Ethylene or Equivalent Compounds



reagent	conditions	Yield
$CH_2{=}CH_2$, 7.5 bar	toluene, 90 °C	25%
$CH_2{=}CH{-}OBz$	CH_2Cl_2, NMO, rt	19%
$CH_2{=}CH{-}OAc$	CH_2Cl_2, NMO, rt	22%
$CH_2{=}CH_2$, 6 bar	Tol/MeOH, NMO, rt	46%
$CH_2{=}CH_2$, 6 bar	CH_2Cl_2, NMO, rt	54%
$CH_2{=}CH_2$, 6 bar	CH_2Cl_2, 4 Å MS, NMO, rt	67%

6−8 bar pressure of ethylene gave only 25% yield of the desired product, but we were delighted to see that the

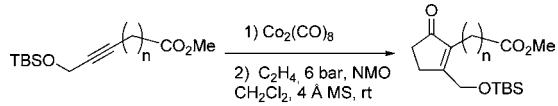
(7) Loeffler, C.; Berger, S.; Guy, A.; Durand, T.; Bringmann, G.; Dreyer, M.; Von Rad, U.; Durner, J.; Mueller, M. *J. Plant Physiol.* **2005**, *137*, 328.
(8) Thoma, I.; Krischke, M.; Loeffler, C.; Mueller, M. J. *Chem. Phys. Lipids* **2004**, *128*, 135.
(9) (a) Imbusch, R.; Mueller, M. J. *Free Radical Biol. Med.* **2000**, *28*, 720. (b) Imbush, R.; Mueller, M. J. *Plant Physiol.* **2000**, *124*, 1293.
(10) Reviews on the synthesis of prostaglandins and analogues: (a) Das, S.; Chandrasekhar, S.; Yadav, J. S.; Gree, R. *Chem. Rev.* **2007**, *107*, 3286. (b) Sheddan, N. A.; Czybowski, M.; Mulzer, J. *Chem. Commun.* **2007**, 2107.
(11) Selected syntheses of prostanes B_1: (a) Schmidt, A.; Boland, W. *J. Org. Chem.* **2007**, *72*, 1699. (b) El Fangour, S.; Guy, A.; Vidal, J.; Rossi, J.; Durand, T. *J. Org. Chem.* **2005**, *70*, 989. (c) Mikolajczyk, M.; Midura, W. H.; Ewas, A. M. M.; Perlikowska, W.; Mikina, M.; Jankowiak, A. *Phosphorus, Sulfur* **2008**, *183*, 313. (d) Mikolajczyk, M. *Phosphorus, Sulfur* **2002**, *177*, 1839. (e) Mikolajczyk, M.; Mikina, M.; Jankowiak, A. *J. Org. Chem.* **2000**, *65*, 5127. (f) Hyuga, S.; Hara, S.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2303. (g) Naora, H.; Onuki, T.; Nakamura, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2859.
(12) Other Pauson−Khand routes to prostanes: (a) Mulzer, J.; Graske, K. D.; Kirste, B. *Liebigs Ann. Chem.* **1988**, 891. (b) Iqbal, M.; Evans, P.; Lledó, A.; Verdaguer, X.; Pericàs, M. A.; Riera, A.; Loeffler, C.; Sinha, A. K.; Mueller, M. J. *ChemBioChem* **2005**, *6*, 276. (c) Iqbal, M.; Duffy, P.; Evans, P.; Cloughley, G.; Allan, B.; Lledó, A.; Verdaguer, X.; Riera, A. *Org. Biomol. Chem.* **2008**, *6*, 4649.

regioselectivity was complete. Our attempts to improve this result by using vinyl acetate and vinyl benzoate as ethylene synthetic equivalents[14] failed (see Table 1). Gratifyingly, when the reaction in DCM was activated by slow addition of *N*-methylmorpholine oxide (NMO),[15] the yield increased to a promising 54%. The reaction was very clean: the main byproduct was the starting acetylene **3**, which was formed by decomplexation of the cobalt complex due to the low concentration of ethylene. We reasoned that the use of molecular sieves, a technique developed by Perez-Castells,[16] could be beneficial since absorption of ethylene by the sieves would increase the amount of available olefin. We were pleased to find that addition of powdered 4 Å molecular sieves improved the yield to 67%.

The syntheses of PGB_1 and PPB_1 type I required preparation of the internal alkynes **5a** and **5b**, respectively, which were easily synthesized from propargyl alcohol and the corresponding bromo acid[17] in excellent yields.

The alkynes **5a** and **5b** were treated with octacarbonyl dicobalt in hexanes to give the corresponding cobalt complexes, which were then submitted to the previously developed Pauson−Khand conditions. The reactions were performed in a pressure reactor under ethylene (6 bar) at room temperature. Powdered 4 Å molecular sieves were added, and the reaction was promoted by consecutive additions of NMO. As expected, good yields were obtained with remarkable reliability in both cases (Scheme 1).

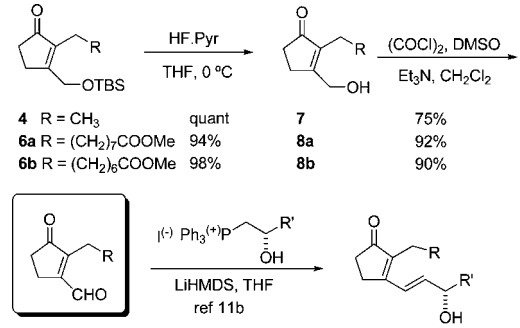
Scheme 1. Pauson−Khand Syntheses of the Cyclopentenones **6a** and **6b**



5a	n = 7	69%	**6a** n = 7
5b	n = 6	70%	**6b** n = 6

With the Pauson−Khand adducts in hand, we then studied their transformation into the corresponding aldehydes. We first attempted removal of the silyl protecting group in **4** using TBAF, but the yields were disappointingly low. Gratifyingly, treatment with fluorohydric acid in acetonitrile gave the desired alcohol **7** in 63% yield. Interestingly, using HF•Pyr, **7** was obtained in quantitative yield. The optimized procedure was also applied to the cyclopentenones **6a** and **6b** with equal results. The final oxidation was readily performed under Swern conditions, affording the desired aldehydes **9**, **10a**, and **10b** in excellent yields (Scheme 2).

Scheme 2. Transformation of the Pauson−Khand Adducts into the Key Aldehydes: Formal Syntheses of PPB_1 Type II and PPB_1 Type I



4	$R = CH_3$	quant	**7**	75%
6a	$R = (CH_2)_7COOMe$	94%	**8a**	92%
6b	$R = (CH_2)_6COOMe$	98%	**8b**	90%

9	$R = CH_3$	23%
10a	$R = (CH_2)_7COOMe$	29%
10b	$R = (CH_2)_6COOMe$	-

PPB_1-II **(1)** $R' = (CH_2)_7$-COOMe
PPB_1-I **(2a)** $R' = CH_2$-CH_3
PGB_1 **(2b)** $R' = (CH_2)_3$-CH_3

Conversion of aldehydes **9** and **10a** into the methyl esters of phytoprostanes PPB_1 type II (**1**) and PPB_1 type I (**2a**), respectively, had already been reported by Durand.[11b] As such, our preparations are very short formal syntheses of these compounds. However, since—to the best of our knowledge—conversion of aldehyde **10b** into PGB_1 had never been reported, we decided to introduce the aliphatic ω-side chains in **10a** and **10b** to complete the syntheses of PPB_1 type I (**2a**) and PG-B_1 (**2b**). The synthesis of PPB_1 type II, already described by Durand,[11b] was excluded because it involved a less accessible reagent. It should be noted that olefination of aldehydes such as **9** and **10** was reported to be especially difficult. For example, the Wittig−Horner reaction with a keto-phosphonate gave the corresponding keto-PGB_1 in low yield.[18] In our hands, the Wittig olefination of **10a** described by Durand afforded the desired phytoprostane in low yield as a mixture of stereoisomers that were difficult to separate. This prompted us to explore other olefination procedures to introduce the chiral side chain. Namely, we decided to use the Julia olefination and to protect the hydroxyl as a *tert*-butyldimethylsilyl ether (TBS) to facilitate the purification of the product.

Preparation of the Julia reagent **11**, required for the synthesis of PPB_1 type I from aldehyde **10a**, is depicted in Scheme 3. Commercially available (*S*)-1,2-epoxybutane was reacted with 2-mercaptobenzothiazole (BTSH) to give the thioether **12**, which was in turn oxidized to the sulfone **13** with H_2O_2 in the presence of catalytic amounts of $MnSO_4$•H_2O.[19] The TBS protecting group was introduced

(13) Robert, F.; Milet, A.; Gimbert, Y.; Konya, D.; Greene, A. E. *J. Am. Chem. Soc.* **2001**, *123*, 5396.

(14) (a) Kerr, W. J.; McLaughlin, M.; Pauson, P. L.; Robertson, S. M. *J. Organomet. Chem.* **2001**, *630*, 104. (b) Kerr, W. J.; McLaughlin, M.; Pauson, P. L.; Robertson, S. M. *Chem. Commun.* **1999**, 2171.

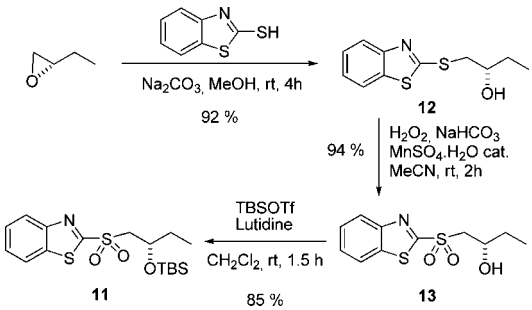
(15) Pauson−Khand reactions with ethylene: (a) Donkervoort, J. G.; Gordon, A. R.; Johnstone, C.; Kerr, W. J.; Lange, U. *Tetrahedron* **1996**, *52*, 7391. (b) Gordon, A. R.; Johnstone, C.; Kerr, W. J. *Synlett* **1995**, 1083. (c) Rautenstrauch, V.; Megard, P.; Conesa, J.; Kuester, W. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1413.

(16) (a) Perez-Serrano, L.; Casarrubios, L.; Dominguez, G.; Perez-Castells, J. *Org. Lett.* **1999**, *1*, 1187. (b) Blanco-Urgoiti, J.; Dominguez, G.; Perez-Castells, J. *Synthesis* **2004**, *3*, 182.

(17) Rao, A.; Reddy, E.; Purandare, A.; Varaprasad, Ch. *Tetrahedron* **1987**, *43*, 4385.

(18) Martin, I.; Anvelt, J.; Välime, T.; Pehk, T.; Lille, U. *Synth. Commun.* **1990**, *20*, 2597.

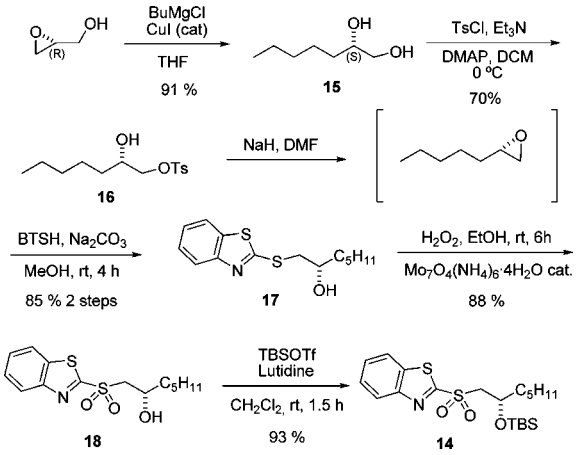
Scheme 3. Preparation of the Julia Reagent **11** for the Synthesis of PPB_1 Type I



under standard conditions to give **11** in excellent yield (Scheme 3).

Likewise to **11**, sulfone **14**, the Julia reagent necessary for the synthesis of PGB_1, was readily prepared as shown in Scheme 4. Commercially available (*R*)-glycidol was

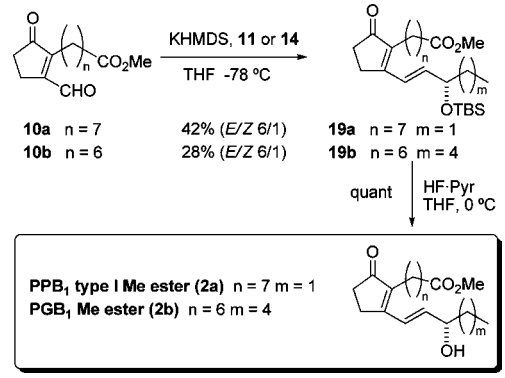
Scheme 4. Preparation of the Julia Reagent **14** for the Synthesis of PGB_1



reacted with an excess of *n*-butylmagnesium chloride under copper catalysis to give the enantiomerically pure diol **15**, which was converted into the terminal epoxide by tosylation of the primary alcohol, followed by treatment with NaH in DMF. The resulting chiral epoxide was treated in situ with BTSH to give the thioether **17**, which was later oxidized to the sulfone **18**. As before, protection of the hydroxyl group as *tert*-butyldimethylsilyl ether afforded the Julia reagent **14** in excellent yield. Unfortunately, the instability of the sulfones prevented their use under premetalation conditions in the Julia reaction. Thus, when sulfone **11** was treated with base at −78 °C, and the reaction was quenched with water after 2 h, we observed mostly decomposition products as well as a small amount of olefin derived from the elimination of the *tert*-butyldimethylsilyloxy group in the reaction crude. However, we were pleased to find that under Barbier conditions, reaction of aldehyde **10a** with sulfone **11** using KHMDMS as base afforded **19a** in 42% yield (*E*/Z 6:1). Despite the moderate yield, we were pleased that both *E*- and *Z*-protected PPB_1 type I were easy to purify by standard flash chromatography. Moreover, the TBS group in **19a** was removed in quantitative yield upon treatment with HF·Pyr, affording **2a**, which is spectroscopically identical to the product described by Durand.[11b]

Similarly to **2a**, the protected prostaglandin PGB_1 **2b** was obtained from aldehyde **10b** and sulfone **14**. Although the yield of the Julia reaction was low, the protected product **19b** was again readily purified and cleanly afforded PGB_1 methyl ester **2b** upon treatment with HF·Pyr (Scheme 5).

Scheme 5. Final Steps in the Syntheses of PG-B_1 and PPB_1 Type I Methyl Esters



In summary, we have developed a new enantioselective approach to prostaglandin and phytoprostanes B_1 by intermolecular Pauson−Khand reactions of silyloxymethyl acetylenes as a key step. These reactions, promoted by NMO in the presence of molecular sieves, proceed in good yields and complete regioselectivity. We have also studied the use of a Julia reaction to introduce the chiral side chains in PGB_1 and PPB_1 type I. Although the yields of the olefinations were low, the TBS protected products were easy to purify and afforded methyl esters **2a** and **2b** in quantitative yield. Our synthetic approach is extremely short and convergent, affording the key aldehydes in only three high-yielding steps from readily available acetylenes.

Acknowledgment. We thank MICINN (CTQ2008-000763) for financial support. A.V. thanks IRB Barcelona and MICINN for a fellowship.

Supporting Information Available: Experimental procedures and characterization of compounds **2a**, **2b**, **4**−**14**, and **17**−**19**. ^1H and ^{13}C NMR spectra of compounds **2a**, **2b**, **4**−**14**, and **17**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901213D

(19) Alonso, D. A.; Nájera, C.; Varea, M. *Tetrahedron Lett.* **2002**, *43*, 3459.