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General Approach to Prostanes B_1 by Intermolecular Pauson–Khand Reaction: Syntheses of Methyl Esters of Prostaglandin B_1 and Phytoprostanes 16-B_1-PhytoP and 9-L_1-PhytoP

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A synthetic approach to the methyl esters of Prostaglandin B_1 and Phytoprostanes 16-B_1-PhytoP (PPB_1-I) and 9-L_1-PhytoP (PPB_1-II) based on the modified Julia olefination of a formylcyclopentenone and an appropriately protected hydroxy sulfone has been developed. The cyclopentenones were efficiently prepared by intermolecular Pauson–Khand reaction of a (silyloxymethyl)alkyne. The sulfone counterpart was prepared by regioselective ring-opening of the appropriate chiral epoxides by 2-mercaptobenzothiazole. The protecting group for the alcohol functionality on the sulfone proved to be crucial. Protection as a *tert*-butyl ether was the best solution, giving better results than a *tert*-butyldimethylsilyl ether.

Introduction

Polyunsaturated fatty acids (PUFAs) are key constituents of all organisms, and they have a large number of biological functions.[1] They are precursors of a wide variety of essential signaling molecules, mediators, and biologically active secondary metabolites. Arachidonic acid is one of the most important PUFAs, due to the significance of the compounds derived from its enzymatic and non-enzymatic metabolism, such as the prostaglandins and isoprostanes. These hormone-like compounds[2] have a 20-carbon skeleton and have many crucial functions that are implicated in many diseases.[3] Some naturally occurring prostaglandins and several synthetic analogs are well-known drugs.[4] Prostaglandin B_1 (PGB_1; Figure 1) is formed by non-enzymatic dehydration of PGE_1. PGB_1 has an affinity for peroxisome-proliferator-activated receptor-γ (PPAR-γ), which is involved in fat deposition and metabolism. Moreover, its oligomers have high anti-oxidant and ionophoric activity.[5]

Phytoprostanes (PPs) are prostaglandin analogs found in plants.[6] They are formed by a non-enzymatic mechanism from α-linoleic acid, which is the main PUFA present in higher plants. Therefore, phytoprostanes are 18-carbon compounds that differ from prostaglandins in the length of their side-chains. Several classes of PPs are present in plants, and their levels increase under a variety of conditions, especially when free-radical generation is enhanced.[7]

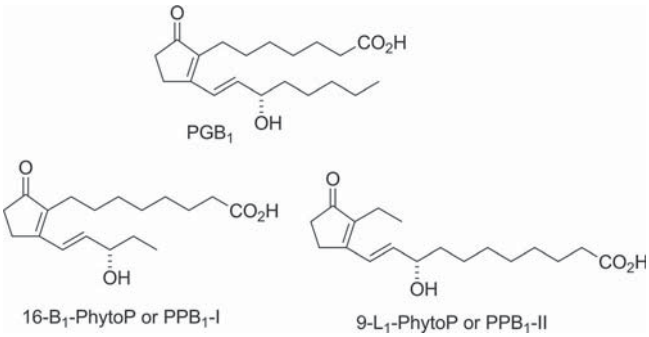

Figure 1. Structures of prostanes B_1.

Moreover, due to their structural similarity to isoprostanes, phytoprostanes interfere with these molecules at the receptor level.[8] It has been proposed that phytoprostanes are components of an oxidant-injury-sensing, archaic signaling system that induces several plant defense mechanisms. Mueller et al.[9] showed that 16-B_1-PhytoP has powerful biological activities, including the activation of mitogen-activated protein kinase (MAPK) and the induction of glutathione-S-transferase (GST), defense genes, and phytoalexins.

The biological relevance of prostanes and the need to assess the physiological activities of these molecules has stimulated research into new methods for their preparation.[10,11] Here we describe the formal syntheses of Phytoprostane 16-B_1 (also known[12] as PPB_1 type I) and Phytoprostane 9-L_1 (also known[12] as PPB_1 type II), as well as of Prostaglandin B_1 (PGB_1) as methyl esters, based on intermolecular Pauson–Khand reactions (PKRs). In our preliminary communication,[13] we reported low yields for the incorporation of the β-side-chain. This was caused by the facile elimination of the silyloxy group under the basic condi-

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