VERSITA

Chemical Papers 67 (6) 631–642 (2013)
DOI: 10.2478/s11696-013-0335-7

ORIGINAL PAPER

Spirocyclisation of phytoalexin 1-methoxybrassinin in the presence of Grignard reagents

[a]Peter Očenáš*, [a]Lucia Tomášová, [a]Peter Kutschy, [b]Pavel Pazdera, [c]Ján Mojžiš, [c]Martina Pilátová

[a] *Department of Organic Chemistry, Institute of Chemical Science, Faculty of Science, P. J. Šafárik University, Moyzesova 11, 040 01 Košice, Slovakia*

[b] *Centre for Syntheses under Sustainable Conditions and their Management, Department of Chemistry, Masaryk University, Kotlářská 2, 611 37 Brno, Czech Republic*

[c] *Department of Pharmacology, Faculty of Medicine, P. J. Šafárik University, SNP 1, 040 66 Košice, Slovakia*

Received 3 October 2012; Revised 27 November 2012; Accepted 1 December 2012

The anti-cancer properties of naturally occurring (2*R*, 3*R*)-(−)-1-methoxyspirobrassinol methyl ether (*I*) and their synthetic amino or piperidyl analogues *II* inspired us to study the synthesis of new target compounds *III* with a C—C bond in the 2-position of indole rather than a C—N or C—O bond (*I* or *II* respectively). The goal was achieved via electrophilic–nucleophilic 3,2-difunctionalisation of 1-methoxybrassinin (*IV*) in the presence of bromine and the Grignard reagent leading to the formation of *cis*- and *trans*-C—C analogues of *I*. Finally, the anti-cancer activities of the new compounds were measured and compared with *I* and *II* in order to show the importance of a heteroatom in the 2-substituted indole on the anti-cancer activity of spirobrassinols.

Keywords: phytoalexins, spirocyclisation, Grignard addition, spiroindolines, anti-proliferative activity

Introduction

Indole phytoalexins are the secondary metabolites isolated from plants of the *Cruciferae* family; they represent an important group of natural compounds due to their importance in the plant protection (Pedras et al., 2011). Spiroindole phytoalexins represent a special group of these compounds, wherein the indole nucleus is spiro-attached to the thiazoline in position C-3 (Kutschy & Mezencev, 2008). Recently, Kutschy et al. (2009) designed and synthesised aryl-amino or piperidyl (Mezencev et al., 2008) analogues *II* of 1-methoxyspirobrassinol methyl ether (*I*) as prospective anti-cancer compounds (Fig. 1).

The amino analogues *II* of *I* were tested for their cytostatic/cytotoxic activity against selected human solid tumour and leukaemia cell lines in vitro. Some of compounds *II* show a biological activity higher than/or comparable to cisplatin on Jurkat cells and they exhibit a higher activity than etoposide on MDA-MB-231 cells (Kutschy et al., 2009). Logically, these promising results invite comparison with alkyl or aryl derivatives of *I*. For this reason, we describe here the original syntheses of *III* and their anti-cancer activity screening test.

Experimental

General

All commercially available reagents were purchased in the highest available purity from Sigma–Aldrich (USA), Merck (Germany), or Acros Organics (Belgium) and used without further purification. Sol-

*Corresponding author, e-mail: peter.ocenas@gmail.com