European Journal of Medicinal Chemistry 45 (2010) 2876–2883

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Design, synthesis and antiproliferative activity of styryl lactones related to (+)-goniofufurone

Velimir Popsavin [a,*], Bojana Srećo [a], Goran Benedeković [a], Jovana Francuz [a], Mirjana Popsavin [a], Vesna Kojić [b], Gordana Bogdanović [b]

[a] Department of Chemistry, Faculty of Sciences, University of Novi Sad, Trg D. Obradovića 3, 21000 Novi Sad, Serbia
[b] Oncology Institute of Vojvodina, Institutski put 4, 21204 Sremska Kamenica, Serbia

ARTICLE INFO

Article history:
Received 10 November 2009
Received in revised form
25 February 2010
Accepted 9 March 2010
Available online 12 March 2010

Keywords:
Styryl lactones
Crassalactone C
Goniofufurone
Antitumour agents
Analogues
Antiproliferatve activity
SAR

ABSTRACT

This paper describes a straightforward divergent synthesis of (+)-goniofufurone mimics (**4**, **5** and **6**) starting from D-xylose. In a preliminary bioassay, analogues **4** and **5** exhibited a submicromolar antiproliferative activity towards HL-60 cells, while the corresponding parent compound **1** was completely inactive against this cell line. At the same time, these molecules showed approximately 10-fold stronger cytotoxicity in the same cell line when compared to the standard anticancer drug doxorubicin (DOX). Analogue **6** displayed 18- and 3-fold higher potency in Raji cell line when compared to control compounds **1** and DOX, respectively. A new divergent route for the preparation of (+)-goniofufurone (**1**) and (+)-crassalactone C (**3**) from D-xylose is also disclosed.

1. Introduction

Phytochemical studies of the genus *Goniothalamus* have resulted in the isolation and characterization of many compounds with a variety of biological activity [1,2]. Due to their proven use in folk medicine in Taiwan, Malaysia, and India to treat rheumatism, edema, as abortifacients, and as mosquito repellents, there has been an interest in the active ingredients as potential therapeutic targets. This resulted in the isolation by McLaughlin et al. [3–5] of a series of styryl lactones which were reported to show antitumour, pesticidal, and embryotoxic activities. Amongst these, (+)-goniofufurone (**1**, Fig. 1) containing a furano-furone bicyclic core has shown significant cytotoxic activities against several human tumour cell lines [6,7]. Due to its unique and intriguing structure, as well as its promising antitumour activity this natural product along with a number of its analogues has attracted the attention of many synthetic groups [8–18]. We have been involved in the synthesis of bio-active natural products and analogues having γ-lactone rings and have recently accomplished the total synthesis of a number of styryl lactones by chirality transfer from D-xylose [19–21]. In continuation of this strategy, we report herein on the synthesis and preliminary in vitro antitumour screening of new styryl lactones **4**, **5** and **6** as possible (+)-goniofufurone mimics. Compound **4** was designed as a conformationally flexible analogue of (+)-goniofufurone (**1**) and may be formally derived from **1** through a cleavage of the C_3–O_6 bond. In the same time, molecule **4** represents a 3-deoxy derivative of (+)-cardiobutanolide (**2**), a naturally occurring styryl lactone that was recently isolated from the stem bark of *Goniothalamus cardiopetalus* [22]. Both furano-lactones **5** and **6** were designed as less polar analogues of (+)-goniofufurone (**1**). Enhanced lipophilic character of **5** and **6** should improve their cell membrane permeation that may be beneficial for their antitumour activity. On the other hand, molecule **5** might be considered as a non-vinylogous analogue of (+)-crassalactone C (**3**), the naturally occurring styryl lactone that was very recently isolated from the leaves and twigs of *Polyalthia crassa* [23]. Apart from the synthesis of **4**–**6**, a novel divergent route to **1** and **3** was also developed in order to provide samples of the leads that would serve as positive controls in antitumour assays.

* Corresponding author. Tel.: +381 21 485 27 68; fax: +381 21 454 065.
E-mail address: velimir.popsavin@dh.uns.ac.rs (V. Popsavin).

0223-5234/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2010.03.010

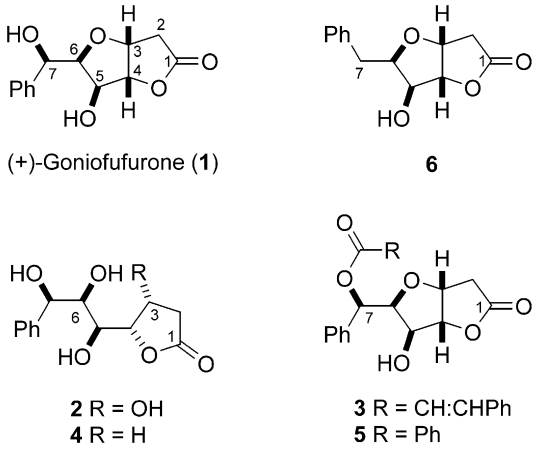


Fig. 1. Naturally occuring styryl lactones and analogues.

2. Results and discussion

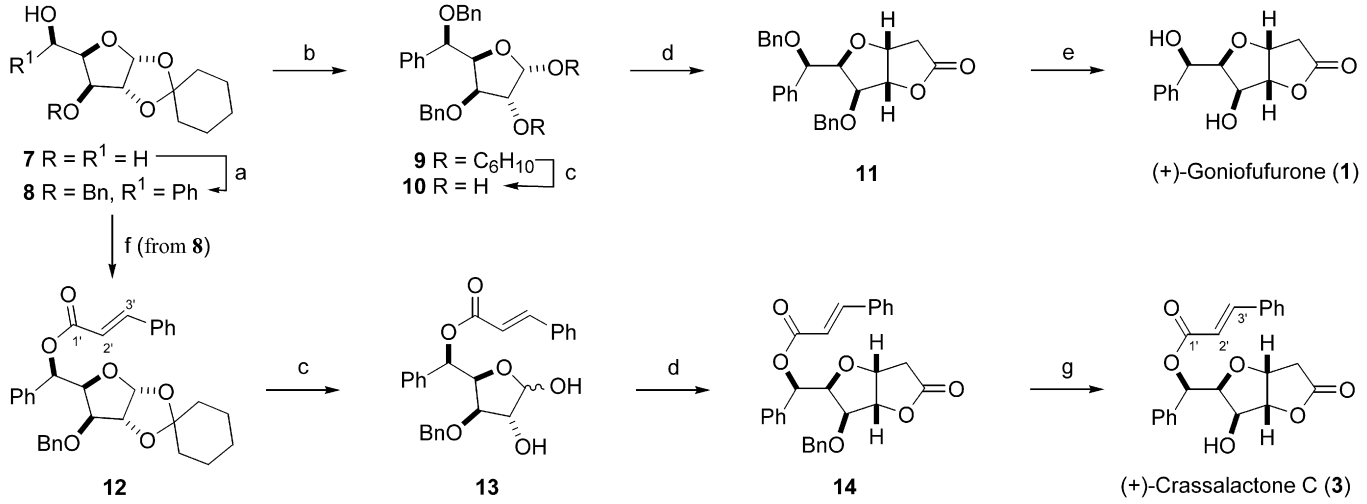
2.1. Chemistry

The divergent synthesis of natural products **1** and **3** is outlined in Scheme 1. The known [20,21] alcohol **8** that is readily available from partially protected D-xylose derivative **7** [24], was conveniently used as a common intermediate for the preparation of both targets **1** and **3**.

For the sake of synthesis of **1**, compound **8** was first converted to the corresponding di-*O*-benzyl ether **9** (94%) by treatment with BnBr (NaH, DMF). Hydrolytic removal of the cyclohexylidene protective group in **9** with aqueous acetic acid gave a 69% yield of the known lactol **10**, with physical constants (mp and optical rotation) in good agreement with those previously reported [25]. Compound **10** may be converted to the target **1** via the reported two-step sequence which consists of a *Z*-selective Wittig olefination, followed by hydrogenolytic removal of both benzyl ether protective groups [25]. However, we wanted to explore an alternative method for elaboration of the required [3.3.0] bicyclic lactone core based on the condensation of **10** with Meldrum's acid [26]. Accordingly, compound **10** was allowed to react with Meldrum's acid in DMF, in the presence of Et_3N, whereupon the protected lactone **11** was obtained in 73% yield. Intermediate **11** was finally converted to (+)-goniofufurone (**1**) after hydrogenolytic removal of both benzyl protective groups (H_2-Pd/C, MeOH). This synthetic sequence, which produced the target **1** in 35% overall yield (from **8**), is somewhat less efficient with respect to that previously completed in our laboratory (43% overall yield) [20,21]. The physical and spectroscopic data of thus prepared sample **1** are in good agreement with the literature values [18].

The synthesis of (+)-crassalactone C (**3**) commenced with a conversion of **8** into the corresponding 5-*O*-cinnamoyl derivative **12**. Accordingly, compound **8** was treated with cinnamic acid and DCC, in anhydrous CH_2Cl_2 and in the presence of DMAP, to afford an almost quantitative yield of **12**. The intermediate **12** was converted to the protected lactone **14** by using the same methodology as that already applied for the conversion of **9**–**11**. Thus, treatment of **12** with aqueous acetic acid gave the expected lactol **13** (73%), while the concomitant condensation of **13** with Meldrum's acid furnished **14** in 73% yield. Moreover, oxidative cleavage [27] of the benzyl protecting group in **14** (DDQ, $CHCl_3$, H_2O) gave (+)-crassalactone C (**3**), with physical and spectral properties in full agreement with those previously reported [20,21,23]. This new synthesis of **3** proceeds in eleven linear steps with 15.2% overall yield calculated to starting D-xylose derivative **7**. The preceding preparation of **3** was accomplished in 7.8% overall yield over ten linear steps [20,21].

The synthesis of analogues **4**, **5** and **6** is shown in Scheme 2. The known [20,21] 5-*O*-benzoyl derivative **15** has served as a convenient starting compound for the preparation of both targets **4** and **5**, via the lactol **16** as a common intermediate. Thus, hydrolytic removal of the cyclohexylidene protective group in **15** with diluted acetic acid, gave the lactol **16** (78%). Wittig olefination of **16** with $Ph_3P{=}CHCO_2Me$ in DMF took place stereoselectively to afford the (*E*)-unsaturated ester **17** in 69% yield. Catalytic hydrogenation of **17** over 10% Pd/C in methanol yielded the saturated ester **18** (72%). Sodium methoxide *O*-debenzoylation of **18** occurred with concomitant lactonisation to afford the target **4** ready for biological testing.



Scheme 1. Reagents and conditions: (a) Ref. 20, 33.8% from 7 steps; (b) BnBr, NaH, DMF, 0 °C for 1 h, then rt for 0.5 h, 94%; (c) 70% aq AcOH, reflux, 5 h for **9**, 69% of **10**, 12 h for **12**, 73% of **13**; (d) Meldrum's acid, Et_3N, DMF, 46–48 °C, 72 h for **10**, 73% of **11**, 65 h for **13**, 73% of **14**; (e) H_2-Pd/C, MeOH, rt, 9 days, 74%; (f) cinnamic acid, DCC, DMAP, CH_2Cl_2, rt, 24 h, 97%; (g) DDQ, 10:1 $CHCl_3/H_2O$, reflux, 30 h, 87%.