Tetrahedron 70 (2014) 4022–4030

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total synthesis of fuzinoside

Ping He [a], Xiao-Huan Li [a], Qiao-Hong Chen [b,*], Jing-Song Yang [a], Feng-Peng Wang [a,*]

[a] Department of Chemistry of Medicinal Natural Products, West China College of Pharmacy, Sichuan University, No. 17, Duan 3, Renmin Nan Road, Chengdu 610041, PR China
[b] Department of Chemistry, California State University Fresno, 2555 E. San Ramon Avenue, M/S SB70, Fresno, CA 93740, USA

ARTICLE INFO

Article history:
Received 26 December 2013
Received in revised form 8 April 2014
Accepted 24 April 2014
Available online 2 May 2014

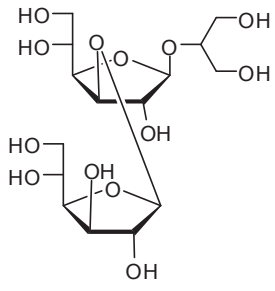
Keywords:
Fuzinoside
D-Galactose
Cardiac activity

ABSTRACT

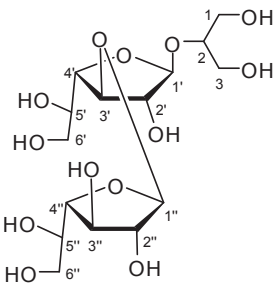
The first total syntheses of fuzinoside (**1b**) were achieved from D-galactose through two strategies (BCA and ABC) in 11 (total yield: 5.0%) and 15 (total yield: 3.7%) steps, respectively. Comparison of NMR data of synthetic compound **1b** and those of the fuzinoside isolated from the lateral roots of *Aconitum carmicaelii* suggests that the structure reported in the literature[1,2] might not be accurate. The synthetic fuzinoside (**1b**) exhibited moderate cardiac activity in the isolated bullfrog heart assay.

1. Introduction

Fuzinoside (**1a**), glycerol β-D-galactofuranosyl-(1→3)-β-D-galactofuranoside, was isolated from the lateral roots of *Aconitum carmicaelii* in 2004.[1,2] Fuzinoside has been demonstrated to have apparent cardiotonic effect,[1] which might be associated with its ability to enhance the amount of calcineurin (CaN) based on the in vivo data in rats.[3] The extreme scarcity of fuzinoside precluded a comprehensive evaluation of its biological profile and structure–activity relationship studies. Consequently, total synthesis of fuzinoside is in need. It should be noted that the structure for fuzinoside (**1a**)[1,2] should be redrawn as **1b** in correspondence with its name, glycerol 1-2-*O*-β-D-galactofuranosy-1-3-β-D-galactonoside. In the present paper, we wish to report the first total syntheses of fuzinoside via two synthetic strategies. The first strategy is designated as BC+A route: synthesis of a 1→3-disaccharide followed by glycosylation with glycerine. The second strategy is designated as AB+C route: synthesis of glycerol-β-D-galactose via O-glycosylation followed by incorporation of another molecular of D-galactose (Scheme 1). The total yields for the syntheses of fuzinoside via two synthetic routes are 5.0% and 3.7%, respectively.



1a Fuzinoside
(The structure in the literature)



1b Fuzinoside

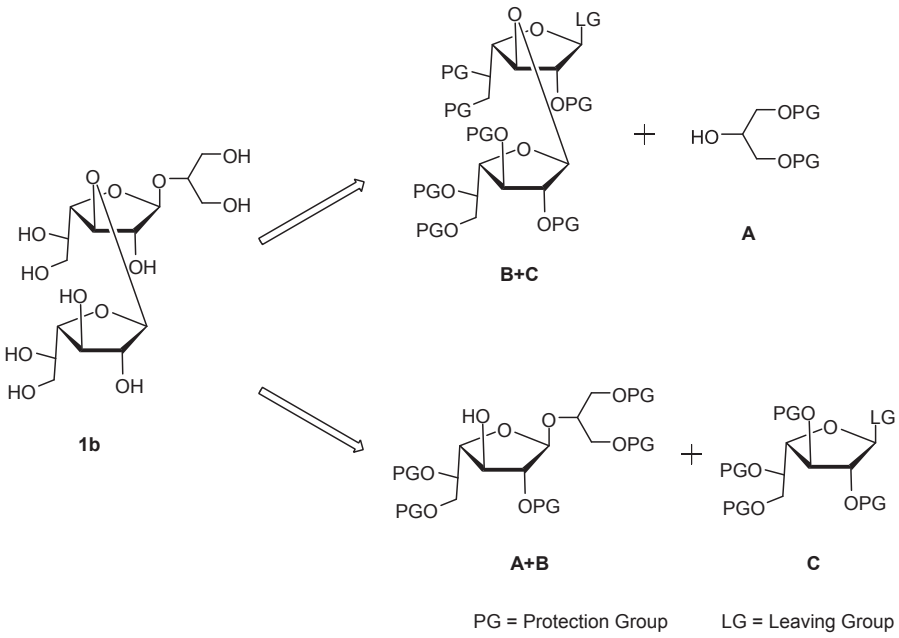
2. Results and discussion

2.1. BCA synthetic strategy

According to the method described in the literature,[4,5] compounds **3** and **4** were made by treatment of glycerin with benzaldehyde dimethyl acetal/TsOH and TrCl/pyridine, respectively. Thioglycoside **5**

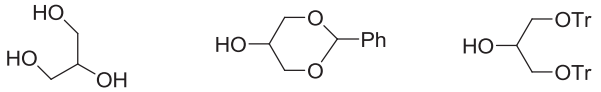
* Corresponding authors. Tel./fax: +86 28 85501368; e-mail addresses: qchen@csufresno.edu (Q.-H. Chen), wfp@scu.edu.cn (F.-P. Wang).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.04.069



Scheme 1. Two synthetic strategies for fuzinoside.

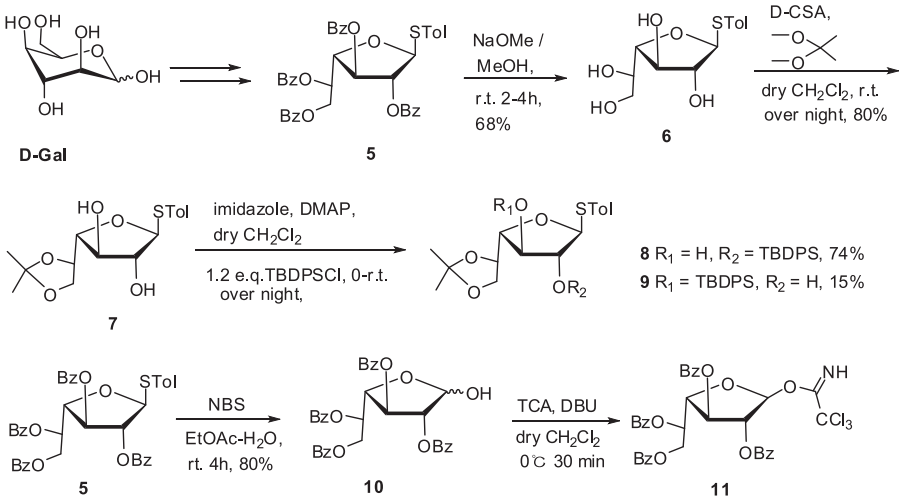
was prepared in 40% yield from D-galactose using a four-step reaction procedure as described in the literature.[6]



2 **3** **4**

Hydrolysis of **5** with 1% sodium methoxide in methanol at rt for 2–4 h afforded fully hydrolyzed product **6**. Protection of C5–C6 diol in **6** by reacting with 2,2-dimethoxypropane catalyzed by D-camphorsulfonic acid gave compound **7**.[6,7] Reaction of **7** in anhydrous dichloromethane with 1.2 equiv of TBDPSCl in the presence of DMAP and imidazole for 10 h yielded 2-*O*-TBDPS ether **8** (major product, 74%) and 3-*O*-TBDPS ether **9** (minor product, 15%)[8] (Scheme 2). Deprotection of C-1 of compound **5** with NBS/EtOAc–H_2O yielded **10**, which was treated with trichloroacetonitrile in the presence of DBU to give **11**.[6] Unfortunately, reaction of **8** and **11** catalyzed by TMSOTf[9] only provided aglycone-transferred product **5** instead of desired product **12** (Scheme 3). Initially, we assumed this might be caused by high reaction temperature or highly reactive TMSOTf. However, the same reaction under much lower temperature (−20 °C, −40 °C, and −78 °C) still generated aglycone-transferred product **5**. Meanwhile, less reactive phenyl thiol ether protected compound **13** was treated with **11** under the same reaction conditions to yield aglycone-transferred compound **15** instead of the expected compound **14** (Scheme 3).

At this point, we considered to replace the thioglycoside with a benzyl protected glycoside, which might enable the glycosylation to proceed smoothly. Compound **16** (β/α=6:1) was prepared from D-galactose according to the procedure described in the literature.[10] Deprotection of silyl groups in compound **16** with TBAF/THF yielded compound **17**. Conversion of **17** to ketal **18** by reacting with 2,2-dimethoxypropane/D-CSA. Selective protection of 2-OH in compound **18** generated compound **19** in high yield by treating with TBDPSCl/DMAP/imidazole in anhydrous dichloromethane overnight.



Scheme 2.