Carbohydrate Research 468 (2018) 51–63

Contents lists available at ScienceDirect

Carbohydrate Research

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

A stereoselective approach towards a small library of cytotoxic isomeric sphingoid bases

Milica Fabišíková[a], Miroslava Martinková[a,*], Jozef Gonda[a], Dominika Jacková[a], Martina Bago Pilátová[b], Juraj Kuchár[c]

[a] Institute of Chemical Sciences, Department of Organic Chemistry, P.J. Šafárik University, Moyzesova 11, 040 01, Košice, Slovak Republic
[b] Institute of Pharmacology, Faculty of Medicine, P.J. Šafárik University, SNP 1, 040 66, Košice, Slovak Republic
[c] Institute of Chemical Sciences, Department of Inorganic Chemistry, P.J. Šafárik University, Moyzesova 11, 040 01, Košice, Slovak Republic

ARTICLE INFO

Keywords:
Sphingolipids
Sphingoid bases
Isomeric dihydrosphingosine
[3,3]-Sigmatropic rearrangements
Olefin cross-metathesis
Antiproliferative/cytotoxic activity

ABSTRACT

Two approaches to a small library of cytotoxic dihydrosphingosine analogues are described. [3,3]-Sigmatropic rearrangements along with an OCM reaction were used as the key steps for the construction of the two isodihydrosphingosines *ent*-**6** and **10**, whereas the functional group manipulations, including Grubbs' metathesis chemistry, were applied to known isothiocyanate scaffolds **15** and **16** to provide access to the enantiomeric forms of *ent*-**6** and **10** and diastereomeric isophytosphingosines *ent*-**7**.HCl and **14**. Cell viability experiments revealed that the target isomeric sphingoid bases were more potent than the traditional anticancer agent cisplatin, with IC_{50} values in the low micromolar range for the most active compounds.

1. Introduction

Sphingoid bases, namely D-*erythro*-sphingosine **1** and D-*ribo*-phytosphingosine **2** (Fig. 1), represent the structural backbone of various groups of more complex sphingolipid molecules and along with their simpler analogues (sphingosine-1-phosphate, ceramide, ceramide-1-phosphate, phytoceramide) intensively participate in cell signaling processes [1]. For that reason, both **1** [2] and **2** [3] have garnered much interest from synthetic chemists in their construction as well as in the synthesis of structurally related naturally occurring congeners termed the 1-deoxysphingoid bases, including spisulosine **3** [4,5], xestoaminol C **4** [4] and clavaminols, the general structure of which is depicted by clavaminol A **5** [4,6] (Fig. 1). It should be noted that these structures demonstrate a remarkable antiproliferative/cytotoxic profile [4] and as such are expected to serve as lead structures [1c] for the design of novel modulators of sphingolipid biosynthesis and/or metabolism [1a,7].

In the search for new analogues of archetypal sphingoid bases such as **1** and **2** with promising anticancer activity based on their ability to interfere with sphingolipid-metabolizing enzymes in malignant cells [1c], synthetic attention has also been focused on the construction of long chain 3-amino-1,2-diols [8a] or 4-amino-1,2,3-triols [9], referred to as isomeric dihydrosphingosines or phytosphingosines, the structures of which are illustrated by compounds **6** [8a] and **7** [9], respectively (Fig. 1). Both of the mentioned types have exhibited significant *in vitro* cytotoxicity [8a,9] and in the case of isodihydrosphingosines also *in vivo* anti-inflammatory activity [8a]. In 2014, Llebaria and Alcaide reported a library of sphingolipid analogues of **1** and/or **2** with different types of nucleophiles at the C-1 position [10], some of which were found to be potent inhibitors of mammalian glucosylceramide synthase and yeast inositol phosphorylceramide synthase. Recently, Davies and co-workers [11] communicated the synthesis of 3-amino-3-deoxy analogues of **1** and **2** (represented by the compounds **8** and **9**, see Fig. 1) with the different vicinal diamino moiety configurations, based on parallel kinetic resolution and double asymmetric induction starting from D,L-serine and L-serine, respectively. It is very probable that their prepared panel sphingoid base derivatives (without protecting groups) can possess potent and selective inhibitory activities towards human sphingolipid enzymes.

In the course of our previous communication [12] on the construction of spisulosine **3**, we accomplished the synthesis of the advanced scaffolds **15** [12] and **16** [12] (Fig. 2) with differently configured amino-alcohol motif from D-isoascorbic acid. In the present work, we would like to describe the preparation two more structurally related congeners **17** and **18** from the same starting material. We envisioned that these four intermediates **15–18** could thus be modified to the corresponding isomeric analogues of **1** and **2**, as illustrated in Fig. 2.

* Corresponding author.
E-mail address: miroslava.martinkova@upjs.sk (M. Martinková).

https://doi.org/10.1016/j.carres.2018.08.008
Received 31 July 2018; Received in revised form 13 August 2018; Accepted 13 August 2018
Available online 16 August 2018

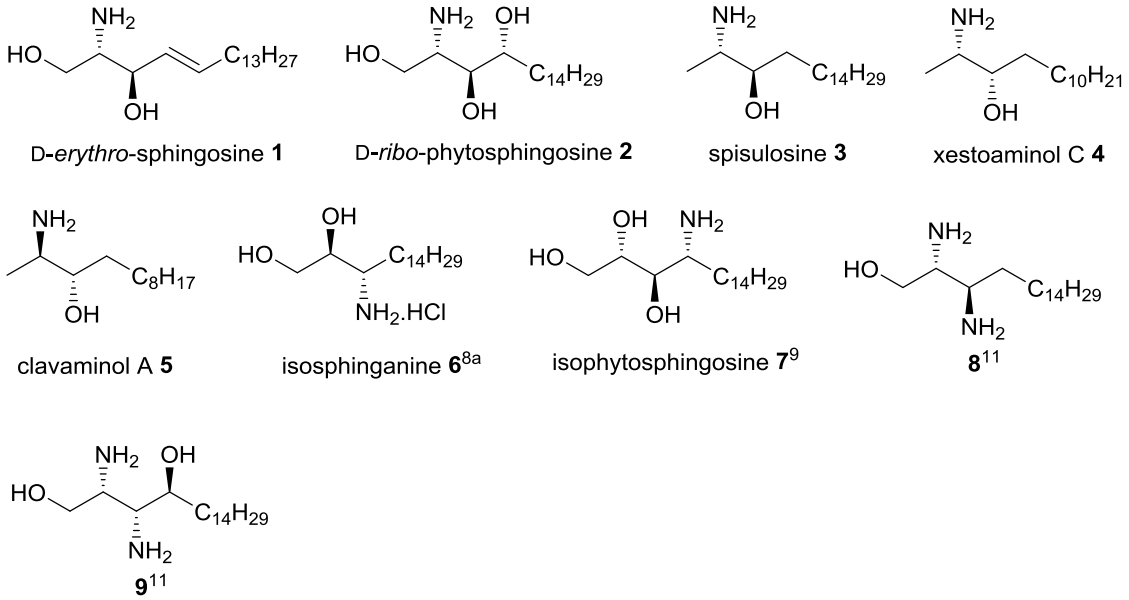


Fig. 1. Structures of the natural sphingoid bases **1**–**5** and their structurally related synthetic analogues **6**–**9**.

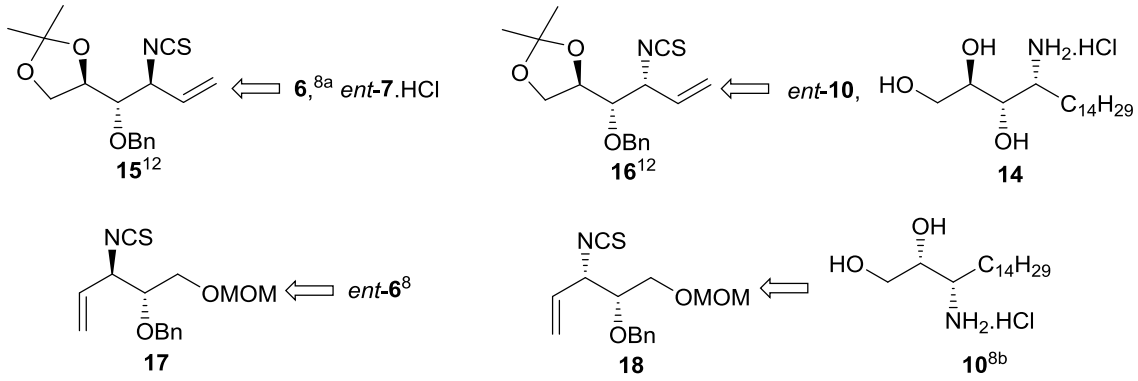


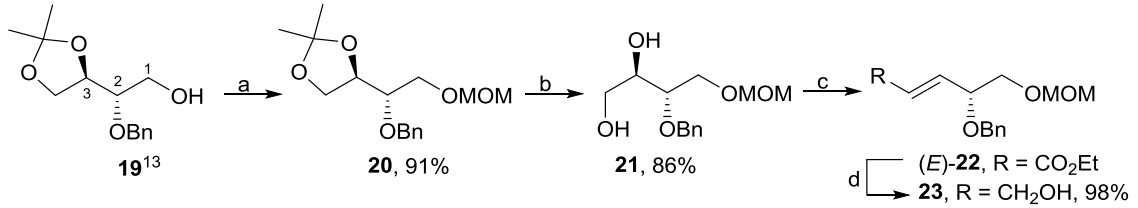
Fig. 2. Our targeted molecules **6**, *ent*-**6**, *ent*-**7**.**HCl**, **10**, *ent*-**10**, **14** and the general approach towards them.

2. Results and discussion

2.1. Chemistry

It should be noted that isothiocyanate frameworks **15** [12] and **16** [12] were prepared on a large scale from the known alcohol **19** [13b], which was derived from D-isoascorbic acid according to the literature protocols [13]. The novel C–N bond in **15** and **16** was installed by a [3,3]-sigmatropic rearrangement at C-1 of the used starting material **19**. On the other hand, in the case of diastereoisomers **17** and **18**, the required stereogenic centre was introduced at C-3 of **19** by the same reaction (*vide infra*). For this purpose, transformation of **19** to **20** (91%) was carried out using MOMCl and Hünig's base in CH_2Cl_2 (Scheme 1). Removal of the acetonide protecting group in methoxymethyl ether **20** was achieved by employing *p*-TsOH in MeOH to provide the corresponding diol **21** (86%). $NaIO_4$ treatment of **21** followed by the Horner-Wadsworth-Emmons olefination afforded α,β-unsaturated esters **22** in 92% yield with an excellent (*E*)-selectivity (*E*:*Z* = 99:1). DIBAL-H reduction of (*E*)-**22** gave the desired allylic alcohol **23** (98%), the construction of which was accomplished over four steps in very good overall yield (71%) from **19** (Scheme 1).

With compound **23** in hand, we next focused our attention on the formation of two templates for the subsequent aza-Claisen rearrangements as the useful carbon-nitrogen bond creating process [14]. As shown in Scheme 2, thiocyanate **24** (91%) was prepared in a two-stage protocol from alcohol **23** by its conversion to the corresponding



Scheme 1. *Reagents and conditions:* (a) MOMCl, DIPEA, CH_2Cl_2, 0 °C→reflux; (b) *p*-TsOH, MeOH, rt; (c) (i) $NaIO_4$, $MeOH/H_2O$, rt; (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C, 92%, (*E*:*Z* = 99:1); (d) DIBAL-H, CH_2Cl_2, −50 °C.