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An efficient synthesis of the polar part of sulfamisterin and its analogs

Miroslava Martinková [a,*], Jozef Gonda [a], Alena Uhríková [a], Jana Špaková Raschmanová [a], Juraj Kuchár [b]

[a] Institute of Chemical Sciences, Department of Organic Chemistry, P.J. Šafárik University, Moyzesova 11, Sk-040 01 Košice, Slovak Republic
[b] Institute of Chemical Sciences, Department of Inorganic Chemistry, P.J. Šafárik University, Moyzesova 11, Sk-040 01 Košice, Slovak Republic

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ABSTRACT

An efficient synthesis of the polar part of sulfamisterin and its analogs starting from D-xylose is described. The corresponding allylic thiocyanates and trichloroacetimidates were subjected to aza-Claisen rearrangement that effectively generated a quaternary carbon having an amino group as one of the substituents. Subsequent functional group interconversions afforded the highly functionalized branched aminopolyol **29** that is expected to have the crucial application in the construction of sulfamisterin. On the other hand, the second diastereoisomer **34** would be transformed to 2-*epi*-congener. With respect to the appropriate stereochemical arrangement, the prepared polar segments **29** and **34** can also be utilized for the synthesis of mycestericins (E, G) and their analogs.

1. Introduction

In recent years, naturally occurring α-substituted α-amino acids such as sphingofungin E and F,[1] mycestericins A–G,[2] sulfamisterin,[3] myriocin,[4] (Fig. 1) have received growing attention as attractive synthetic targets possessing remarkable biological properties. These above-mentioned fungal metabolites, representing a group of sphingolipid-based molecules, are reported to be inhibitors of serine palmitoyltransferase (SPT),[5] a key enzyme involved in the biosynthesis of sphingolipids. Moreover, myriocin[4d,6] and mycestericins A–G[2] have been shown to have a potent immunosuppressive activity with IC_{50} values in the nanomolar range in the mouse allogenic mixed lymphocyte reaction. The common structural feature of these highly functionalized compounds is the quaternary amino acid motif connected with hydroxylated alkyl chain. Due to their unique structure and impressive biological activity, several total syntheses of these antifungal compounds have been developed.[7–10] Our previous success with the construction of α-substituted α-amino acids[9h,11] from sugar molecules suggested that aza-Claisen rearrangement on the structurally appropriate chiral allylic thiocyanates would install the tertiary carbon linked to an amino group precursor and in continuation of the above-mentioned, we decided to extend our methodology to other chiral thiocyanate scaffolds and illustrate their potential for the stereoselective approach to sulfamisterin, mycestericins (E, G) and their 2-*epi*-analogues. Herein we describe the full details of this study that involved both aza-Claisen rearrangements and utilized substrates derived from D-xylose.

2. Results and discussion

As seen from our synthetic plan (Scheme 1), the aza-Claisen rearrangement of chiral allylic thiocyanates **17**–**19** and imidates **14i**–**16i** produced the corresponding isothiocyanates **20a**,**b**–**22a**,**b** and trichloroacetamides **23a**,**b**–**25a**,**b**. These structures represent attractive precursors of the natural α-substituted α-amino acids such as sulfamisterin, mycestericins (E, G) and their analogs. In this respect, the vinyl group of the rearranged products can be transformed to the hydroxymethyl moiety. One of the two protected primary hydroxyl groups is the source of the carboxylic acid group, while the other is necessary for the construction of the non-polar side chain[5g] with C=O and/or C=C functionalities at the required positions via the Wittig reaction or using Grubb's catalyst-mediated olefin cross metathesis.

The known[12b,c] 3,5-di-*O*-benzyl-D-xylofuranose **1** served as the starting material and was easily reached on a large scale, applying modifications of the combined literature protocols.[12] Its oxidative cleavage with $NaIO_4$ in CH_3OH/H_2O and subsequent reduction of in situ generated aldehyde[12c] with $NaBH_4$ afforded alcohol **2** in 96% isolated yield over two steps (Scheme 2). The treatment of **2** with 2,2-dimethoxypropane and catalytic amounts of CSA resulted in the formation of the corresponding isopropylidene derivate **3** (95%, Scheme 2). Catalytic hydrogenation of **3** on 10% Pd–C in EtOH removed the *O*-benzyl protecting groups to give compound **4** in 89% yield (Scheme 2). Its preparation starting with D-xylose was

* Corresponding author. Tel.: +421 55 6228332; fax: +421 55 62342329.
E-mail address: miroslava.martinkova@upjs.sk (M. Martinková).

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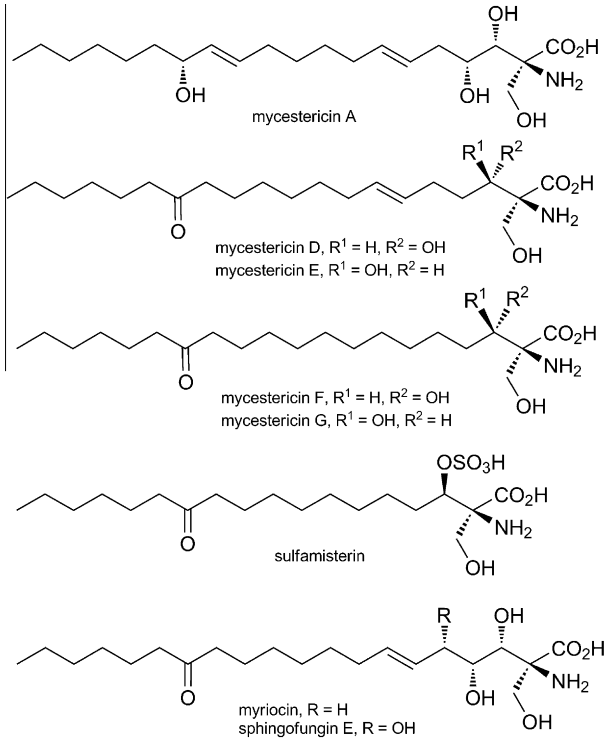
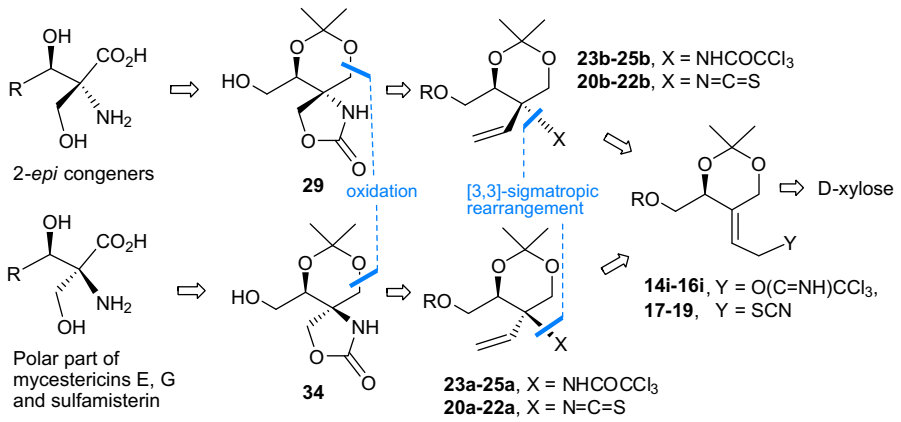


Figure 1. Structures of SPT inhibitors.

achieved through a relatively economic approach in six reaction steps with 48% overall yield. The primary alcohol function present in **4** was selectively protected as *tert*-butyldimethylsilyl, triisopropylsilyl and *tert*-butyldiphenylsilyl ethers using the corresponding silylating reagents (TBDMSCl, TIPSCl and TBDPSCl) and imidazole in dry CH_2Cl_2[13] to furnish **5**, **6**, **7** in 97%, 98% and 98% yields, respectively (Scheme 2). Their oxidation with IBX[14] in acetonitrile gave ketones **8**–**10**, which were subsequently treated with the stabilized ylide ($Ph_3P{=}CHCO_2Et$) to afford (*E*)-α,β-unsaturated esters **11** (98%), **12** (99%), **13** (99%) as the single isomers; the *E*-geometry of the double bonds was determined by NMR spectroscopic analysis, including NOE experiments. Reduction of the ester function in **11**–**13** using standard procedure with DIBAL-H resulted in the formation of allylic alcohols **14**–**16** in 96%, 99% and 91% yields, respectively (Scheme 2). Thiocyanates **17**–**19** were prepared from the corresponding alcohols **14**–**16** by a standard two stage procedure,[11a,b] with very good overall yields (Scheme 2).

With allylic thiocyanates **17**–**19** in hand, we then explored the thermal aza-Claisen rearrangement (Scheme 3), which was carried out in *n*-heptane and *o*-xylene either at 70 °C or at 90 °C under a nitrogen atmosphere to produce the rearranged products **20a**,**b**–**22a**,**b** in very good yields (Table 1), as easily separable mixtures of diastereoisomers; their ratio in the crude reaction mixtures was determined by ^{1}H NMR spectroscopic analysis. The corresponding measurements were performed in $CDCl_3$ and in the case of a mixture of isothiocyanates **20a** and **20b** in C_6D_6 because in $CDCl_3$ solution the necessary proton signals were overlapping and we were not able to assign the diastereomeric ratio. The microwave-promoted[11a,15] thermal [3,3]-sigmatropic rearrangement of thiocyanates **17**–**19** led to significantly shorter reaction times (Table 1), with isolated yields similar to those observed for the thermally driven reaction. The attempted microwave induced rearrangement of thiocyanates **17**–**19** under solvent-free conditions on a silica gel[15a] led only to the decomposition of the starting thiocyanates. The trichloroacetimidates **14i**–**16i**, employed in this study were obtained from allylic alcohols **14**–**16** by a standard procedure (NaH, Cl_3CCN, THF)[16c] and were used immediately in the next step without purification. The thermal Overman rearrangement[17] mediated by microwave irradiation[16a,b] was realized in *o*-xylene in the presence of K_2CO_3[18] either at 170 °C or 190 °C and afforded the corresponding trichloroacetamides **23a**,**b**–**25a**,**b** in good yields (Table 2). Chida and his co-workers[7] described the very similar diastereoselectivity in the thermal Overman rearrangement of imidate derived from (4*R*,2*E*)-2-{4-[(*tert*-butyldiphenylsilyloxy)methyl]-2,2-dimethyl-1,3-dioxan-5-ylidene}ethanol (*ent*-**16**) which was carried out in *o*-xylene in a sealed tube at 140 °C for 48 h. In our cases, the use of microwave irradiation and higher temperatures led to substantial shortening of the reaction times (4.8 or 12 times, see Table 2, entries 5 and 6) compared to the thermal Chida's reaction. The observed diastereoselectivities in the studied aza-Claisen rearrangements were found to be lower or moderate for both the conventional heating and sealed vessel microwave irradiation conditions (Tables 1 and 2). The results summarized in these tables suggest that the ratio of the rearrangements is not influenced by the bulky protecting groups on the primary alcohol function in thiocyanates **17**–**19** and trichloroacetimidates **14i**–**16i** as well as the use of microwave-assisted synthesis had practically no impact on the diastereomeric outcome. In order to rationalize the observed stereoselectivity in the [3,3]-sigmatropic rearrangement, high-level density functional theory (DFT) calculations, which include electron correlation effects were carried out. The solvent effects were also taken into account, in order to obtain a more realistic model of the reaction. Geometries of the transition states were optimized using B3LYP/6-311G(d,p) with JAGUAR 7.7 programme.[19] The nature of vacuum B3LYP transition states was



Scheme 1. Synthetic plan.