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Semisynthetic routes to PF1022H—A precursor for new derivatives of the anthelmintic cyclooctadepsipeptide PF1022A

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ABSTRACT

The cyclooctadepsipeptide PF1022A and its semisynthetic, commercial analogue emodepside show excellent anthelmintic properties. Bis-hydroxy PF1022 (PF1022H), a minor fermentative side-product represents an interesting precursor for new PF1022 related anthelmintics. We report herein two complementary routes which allow a highly efficient conversion of PF1022A to a regioisomeric mixture consisting mainly of the bis-*para* isomer PF1022H and the *meta*–*para* analogue.

1. Introduction

According to the World Health Organization (WHO) parasitic worm infections constitute the most important class of neglected tropical diseases.[1] Those worm infections are a major cause of morbidity and loss of disability-adjusted life years in several underdeveloped African and Asian countries.[2,3] In addition, worm infections cause tremendous health problems and economic losses in livestock and domestic animals. In particular, in the livestock industry, treatment with standard anthelmintics such as the macrolides avermectin and milbemycin or derivatives of these natural products has become problematic due to rapidly developing resistances.[4–6]

The 24-membered cyclooctadepsipeptide PF1022A (**1**, Fig. 1), a metabolite of *Mycelia sterilia* (*Rosselinia* sp.) has been established as the only novel, resistance-breaking anthelmintic during the past two decades. A semi-synthetic analogue of PF1022A, emodepside (**3**), has been introduced recently into the market for the treatment of parasitic helminth infections in companion animals.[4,7]

Structure–activity studies have demonstrated that the two phenyllactic acids are the positions of choice for modifications of PF1022A (**1**).[4,8–13] However, the introduction of functionality into the phenyl rings is far from being trivial. The drastic reaction conditions required to introduce for instance nitro- or sulfonic acid-groups, cause side-reactions and partial decomposition of the macrocycle. Bromine or iodine substituents can be introduced under milder conditions but subsequent Pd-catalyzed cross-coupling reactions to obtain aryl or aryl-substituted derivatives fail completely. The additional synthetic steps needed for the preparation of advanced PF1022A analogs turn out cumbersome and costly.

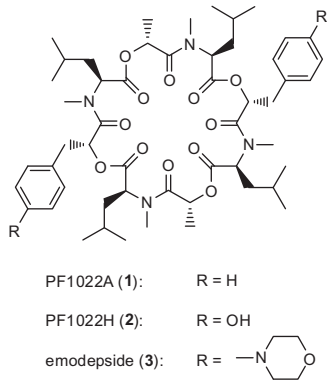

Figure 1. Structures of cyclooctadepsipeptides PF1022A, PF1022H and emodepside.

The bis-hydroxy derivative PF1022H (**2**), a minor side-product in the fermentation process of PF1022A (**1**), might be an interesting alternative. Some lipophilic derivatives of PF1022H (**2**), accessible in only one step, show excellent anthelmintic activities.[8] Unfortunately, PF1022H (**2**) is currently available only in limited amounts from the fermentation broth. Thus, an efficient access to PF1022H (**2**) appears mandatory for the preparation of a larger number of

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screening-compounds needed for the identification of a 'second-generation' PF1022 derived anthelmintic with improved spectrum of activity, drug metabolism and pharmacokinetics.

The most straightforward route to PF1022H (**2**) would be of course a direct hydroxylation of PF1022A (**1**). Unfortunately, standard procedures for the direct hydroxylation of benzene rings such as the $Cu(NO_3)_2$ catalyzed oxidation with H_2O_2 failed completely in our hands.[14] Instead of a one-step hydroxylation of PF1022A (**1**), we established two short sequences which provide PF1022H (**2**) in good to excellent yields.

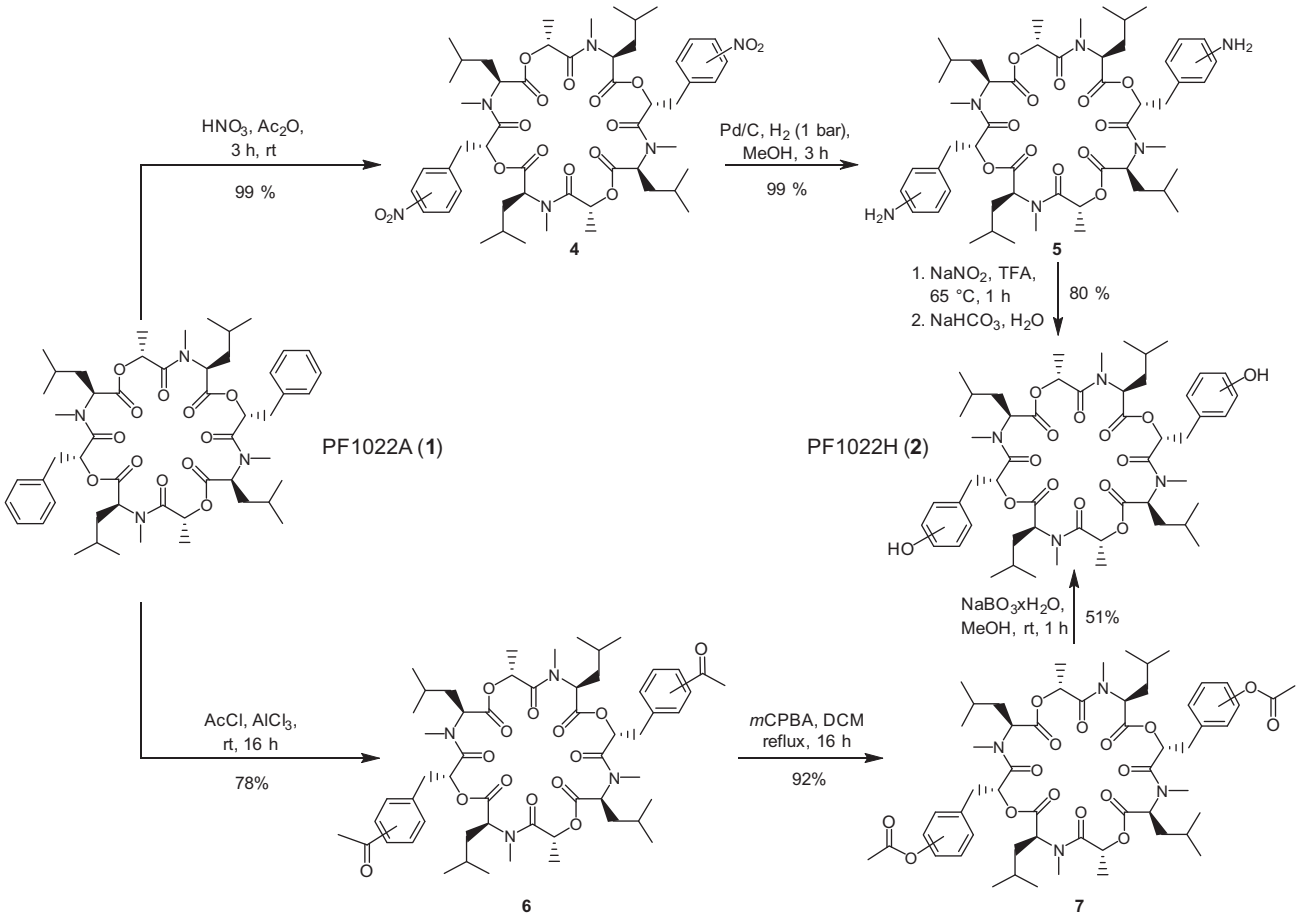
2. Results and discussion

2.1. Route 1: PF1022H by diazotization of bis-amino PF1022 and subsequent hydrolysis

The basic route to bis-amino PF1022 (**5**) and subsequent diazotation has already been described in a previous patent by Nishiyama et al., albeit with remarkably low yields in each step.[15] Based on this basic procedure we developed a process which allows the preparation of PF1022H (**2**) in an excellent yield and gram-amounts. First, PF1022A was nitrated in almost quantitative yield with fumic nitric acid in acetic anhydride (Scheme 1). The regioisomers formed, correspond to bis-*para* nitro-PF1022 (**4**) (45%), followed by the *para–meta* (42%) and *meta–meta* (13%) isomers. Those were not separated since it is known, that the anthelmintic activities of the different regioisomers are similar. The remarkable stability of PF1022A (**1**) against concentrated nitric and also sulfuric acid can be attributed to the *N*-methyl groups which hamper both, oxidation and hydrolysis reactions of the amide functions. Subsequent hydrogenation under standard conditions afforded the bis-amino PF1022 (**5**) again in almost quantitative yield (Scheme 1). Diazotization with $NaNO_2$ in TFA (1 h, 65 °C) followed by a weakly basic hydrolysis with an aqueous $NaHCO_3$ solution afforded in a one-pot reaction the bis-hydroxy PF1022 isomers in 80% yield after chromatographic purification (Scheme 1).

2.2. Route 2: PF1022H by Baeyer–Villiger oxidation of PF1022A and subsequent ester cleavage

One of the few methods which allow the direct introduction of a hydroxy-group in a phenyl-ring under mild conditions is the Baeyer–Villiger oxidation of the corresponding acetophenone which can be obtained easily by a Friedel–Crafts acylation. However, for PF1022A (**1**), the acylation turned out to be troublesome. With the standard Lewis acid $AlCl_3$ and a mixture of acetic anhydride and acetyl chloride in nitromethane or dichloromethane no reaction was observed even with an excess (2–5 equiv) of $AlCl_3$. Other Lewis acids employed for Friedel–Crafts acylations such as $Sc(OTf)_3$,[16] $Bi(OTf)_3$,[17] $Ga(OTf)_3$,[18] $Hf(OTf)_4$,[19] $TiCl_4$, ZnO,[20] $BF_3 \times OEt_2$ or $AlBr_3$ in nitromethane resulted in either no reaction or decomposition of PF1022A (**1**). Even the addition of $LiClO_4$ which is a known Lewis acid activator did not improve the acetylation reaction at all.[19] Remarkably, the 1-methyl-3-ethylimidazolium chloride–aluminum(III) chloride ([EMIM]–$AlCl_3$) ionic liquid which has been described as an exceptionally mild and selective acylation system caused a complete decomposition of the cyclodepsipeptide.[21] As an alternative to the direct acetylation



Scheme 1. Semisynthetis routes to PF1022H.