SHORT COMMUNICATION

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Concise Total Synthesis of Hydrazidomycin A, a Rare Hydrazide Metabolite of *Streptomyces atratus*

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Hydrazidomycins A–C and elaiomycins B–C represent a family of unusual, naturally occurring enehydrazides produced by *Streptomyces* sp. A general synthetic approach to access these densely functionalized hydrazine derivatives is exemplified by the first total synthesis of hydrazidomycin A. The modular synthesis involves a ruthenium-catalyzed hydroamidation of an alkyne and a hydrazide-derived phthalimide to yield predominantly the *Z*-configured enehydrazide.

Introduction

Synthetic hydrazides have long been known for their toxicological and pharmaceutical properties. Examples of clinically relevant therapeutics are the monoamine oxidase inhibitor iproniazid,[1] the antituberculosis agent isoniazid,[1] and benserazide, a decarboxylase inhibitor used in combination with levodopa in the treatment of Parkinson's disease.[2] In stark contrast, natural products featuring hydrazide moieties are extremely rare. We and others have recently discovered the first representatives of a small family of alkyl-substituted hydrazide metabolites. The hydrazidomycins were isolated from cultures of the bacterium *Streptomyces atratus*[3] as congeners of various azoxides.[4] Hydrazidomycins A (**1**), B (**2**), and C (**3**) share a highly substituted hydrazide core and differ only in the chain length of the alkenyl chain and the degree of desaturation in the side chain (Figure 1).[3] Interestingly, hydrazidomycin A (**1**), the simplest of the three trisubstituted hydrazines, showed strong antiproliferative activities.[3] The simultaneously discovered elaiomycins B and C from *Streptomyces* sp. BK 190 were reported as inhibitors of acetylcholinesterase and phosphodiesterase. The structures of hydrazidomycin C (**3**) and elaiomycin C are identical, and the structures of hydrazidomycin B (**2**) and elaiomycin B differ only in the position of the second double bound in the alkenyl chain.[5] Another intriguing natural product containing the unusual trisubstituted enehydrazide moiety is cytotoxic geralcin B (**4**) from *Streptomyces* sp. LMA-545.[6] From the same strain, the mixed hydrazide/azoxide geralcin C (**5**) was isolated, which proved to be active against KB and HCT116 cancer cell lines and to inhibit *E. coli* DnaG primase.[7]

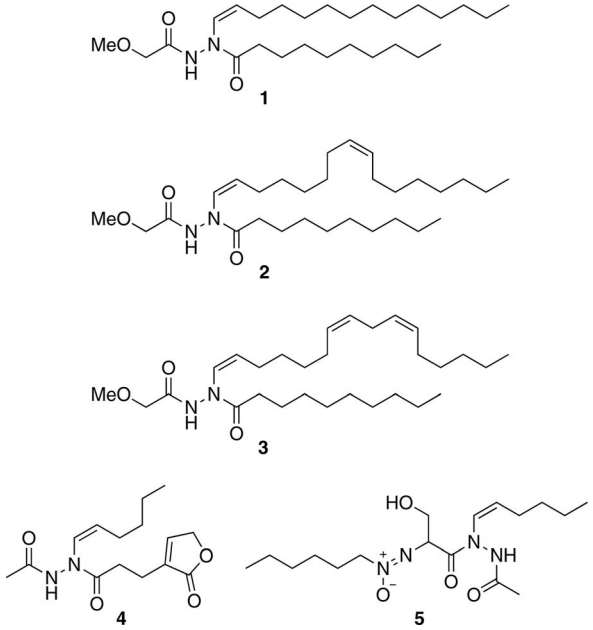

Figure 1. Selected structures of naturally occurring trisubstituted hydrazides: hydrazidomycins A (**1**), B (**2**), and C (**3**) and geralcins B (**4**) and C (**5**).

The hydrazidomycins are interesting targets for synthesis for various reasons. First, the availability of some members of this family is limited because of extremely low production rates (10 $\mu g L^{-1}$ for **1**), which hampers production, isolation, and purification of preparative amounts. Second, the biological activities are diverse, yet nothing is known about structure–activity relationships and mode of actions. Third, the structures appear to be fairly simple, but cur-

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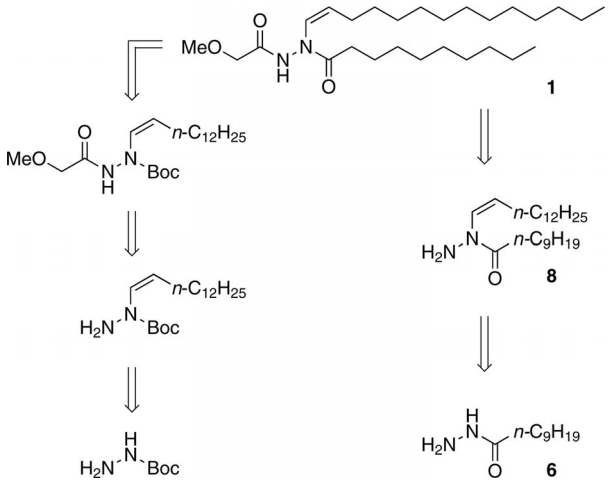
rently no general method for the synthesis of densely functionalized hydrazides is available. Here we report the first total synthesis of the naturally occurring hydrazine derivative hydrazidomycin A (**1**).

Results and Discussion

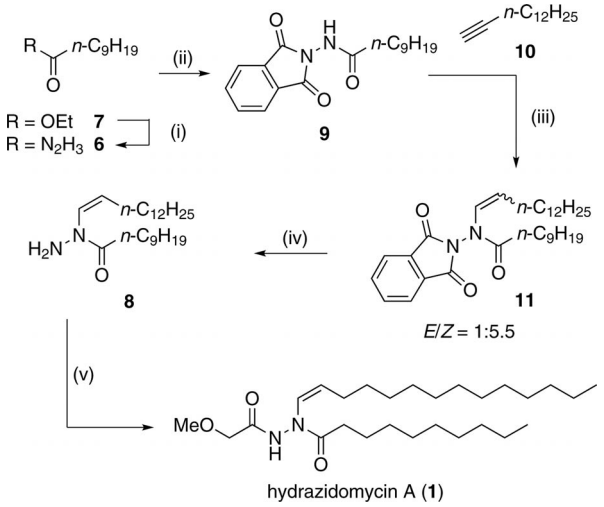
The synthesis of trisubstituted hydrazine derivatives is challenging and requires a well-controlled and selective reaction strategy to avoid multiple alkylations and acylations. Another hurdle is the *Z*-selective synthesis of an enehydrazide moiety. Whereas several synthetic procedures for *N*-alkenylations of hydrazides have been reported, practically all routes start from bis-Boc-protected hydrazines or azodicarboxylates,[8–10] which are unfavorable with respect to downstream transformations required for the synthesis of hydrazidomycins. However, it has been reported that the palladium-catalyzed cross-coupling of *tert*-butyl carbazate with vinyl halides in the presence of cesium carbonate in DMF takes place only at the more acidic N*H*Boc proton (Boc = *tert*-butoxycarbonyl).[10] We reasoned that this protocol would be a suitable starting point for the total synthesis of hydrazidomycin A (**1**), as it would not require additional protection of the NH_2 group and further deprotection steps would be avoided. Thus, we devised the assembly of the *N*-alkenylhydrazine by the Pd-catalyzed cross-coupling of *tert*-butyl carbazate with (*Z*)-tetradecenyl bromide, acylation of the NH_2 function with methoxy acetic acid, followed by deprotection and acylation with decanoic acid (Scheme 1). However, this route was hampered because of unwanted side reactions, and cleavage of the Boc group resulted in an unstable enehydrazine. Thus, we modified the total synthetic strategy in a way that prevented protecting groups at this position. Instead of using *tert*-butyl carbazate, the cross-coupling reaction was performed with decanoic acid hydrazide (**6**), which was easily obtained from ethyl decanoate (**7**) and hydrazine hydrate.[11] However, formation of expected product **8** could not be detected. It seems that the reaction did not take place under the given conditions with less-reactive decanoic acid hydrazide (**6**).



Scheme 1. Retrosynthetic routes to hydrazidomycin A (**1**).

Thus, we envisaged an alternative route by adapting metal-catalyzed protocols that have been established for the synthesis of both *E*- and *Z*-configured enamides.[12–15] We reasoned that a hydrazide-derived phthalimide could be used for the ruthenium-catalyzed hydroamidation of tetradec-1-yne to yield the corresponding alkenylated *Z*-configured product.[15]

First, the free NH_2 function of **6** was protected as phthalimide by heating it at reflux with phthalic anhydride in toluene for several hours.[16] With protected hydrazide **9** in hand, the hydroamidation with tetradecyne (**10**) was accomplished, and indeed, it was possible to obtain *Z*-product **11** with good selectivity (*E*/*Z* = 1:5.5, deduced from the integrals of the NMR signals). To increase the yield, we tested various reaction conditions for the hydroamidation step. However, varying temperature, reaction times, and solvents [DMAC (dimethylacetamide), toluene, DMF/THF] did not improve the efficacy of the reaction. Likewise, applying conditions developed for the *E*-selective alkenylation of amides[14] also did not lead to an improvement in the yield, but instead resulted predominantly in the unwanted *E* isomers. Furthermore, we tested several copper- and palladium-catalyzed coupling reactions[9,10,13] between **9** and (*Z*)-tetradecenyl bromide, but none of these provided access to enehydrazide **11**. Nevertheless, although the yields are not yet satisfactory, it should be noted that this is, to the best of our knowledge, the first report on a ruthenium-catalyzed hydroamidation with the use of a hydrazide to prepare an enehydrazide. Subsequently, the phthalimide was deprotected by using methylhydrazine,[17] and the *E*-configured product was separated by open-column chromatography. Finally, acylation of **8** with methoxyacetic acid under Steg-



Scheme 2. Schematic presentation of the total synthesis of hydrazidomycin A (**1**). Reagents and conditions: (i) $NH_2NH_2{\cdot}H_2O$, EtOH, 24 h, reflux, 83%; (ii) phthalic anhydride, toluene, 3 h, reflux with a Dean–Stark apparatus, 82%; (iii) (cod)Ru(met)$_2$ (cod = 1,5-cyclooctadiene, met = 2-methallyl), 1,4-bis(dicyclohexylphosphanyl)butane, Yb(OTf)$_3$, DMF, 24 h, 60 °C, 11%; (iv) $MeNHNH_2$, THF, 24 h, 0 °C→r.t., 68%; (v) $MeOCH_2COOH$, 4-(dimethylamino)pyridine (DMAP), *N*,*N*′-dicyclohexylcarbodiimide (DCC), CH_2Cl_2, 2 h, r.t., 81%.

lich conditions[18] completed the total synthesis and led to desired product **1** in 81% yield (Scheme 2).

Comparison of the NMR spectra of the natural product confirmed the identity of the compounds. Moreover, both substances elute at the same retention time in the HPLC profile and show similar UV and identical high-resolution mass spectra (see the Supporting Information). Interestingly, duplication of some sets of signals (in particular for the NH and the methine protons) can be observed in the ^{1}H NMR spectra. This phenomenon was also observed for synthetic intermediates such as **8** and **11** and can be explained by the equilibrium between different hydrazide rotamers. Relative to the NMR timescale, the conformational equilibrium is slow at room temperature and therefore allows distinguishing between several isomers.[6,19] Obviously, one of these rotamers dominates in DMSO, which should be a consequence of an additional stabilization resulting from a hydrogen bond between the NH and the carbonyl group of the decanoyl residue (Figure 2).[6] The pronounced low-field shift of the hydrazide proton (δ_{NH} = 10–11 ppm) supports this model.

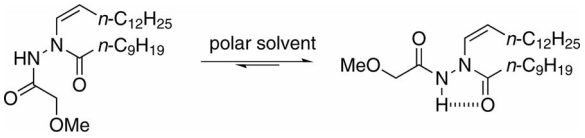


Figure 2. Equilibrium of the rotamers of hydrazidomycin A (**1**) in DMSO.

Conclusions

In this paper the first total synthesis of the naturally occurring hydrazide derivative hydrazidomycin A (**1**) has been reported. The key step of our five-step approach was a ruthenium-catalyzed hydroamidation of alkyne **10** and the protected decanoic acid hydrazide **9** yielding predominantly the *Z*-configured enehydrazide. To best of our knowledge, this is the first time that this protocol was used to synthesize an enehydrazide. This reaction sequence not only allows the synthesis of hydrazidomycin A, but may be used for the preparation of a variety of naturally occurring hydrazides and their derivatives.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and product characterization.

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