

Intramolecular α -acylamino radical cyclizations with acylsilanes in the preparation of polyhydroxylated alkaloids: (+)-lentiginosine, (+)-1,8a-di-*epi*-lentiginosine, and (+)-1,2-di-*epi*-swainsonine

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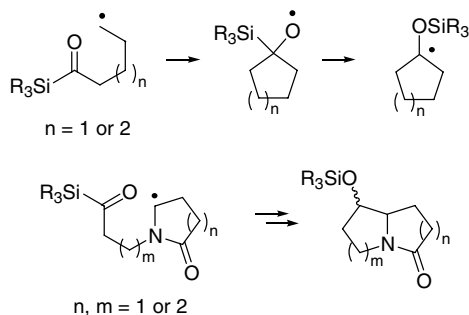
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Abstract—Acylsilanes with latent α -acylamino radical functionality were prepared from different chiral templates. Radical cyclizations of these acylsilanes efficiently constructed polyhydroxylated indolizidine derivatives with excellent stereoselectivity at the bridgehead position. These cyclization products were converted to (+)-lentiginosine, (+)-1,8a-di-*epi*-lentiginosine, and (+)-1,2-di-*epi*-swainsonine.

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1. Introduction

Acylsilanes belong to an interesting class of compounds that displays unusual reactivity.¹ For example, intramolecular radical cyclizations² with acylsilanes as the radical acceptors (Scheme 1) proved to be a useful method in the construction of five- and six-membered cyclic alcohols.³ Several years ago we demonstrated that it was possible to construct silyloxy-substituted pyrrolizidines, indolizidinones, and quinolizidinones via intra-



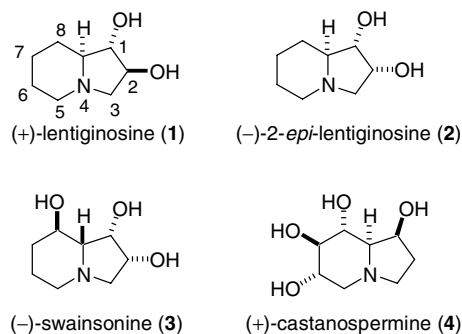
Scheme 1.

Keywords: Acylsilane; Radical cyclization; Lentiginosine; 1,8a-Di-*epi*-lentiginosine; 1,2-Di-*epi*-swainsonine.

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molecular cyclizations of α -acylamino radicals⁴ with acylsilanes (Scheme 1).⁵

Polyhydroxylated alkaloids⁶ (Scheme 2) represented by lentiginosine (**1**), 2-*epi*-lentiginosine (**2**), swainsonine (**3**), and castanospermine (**4**) can be potent and selective glycosidase inhibitors and may be useful as anti-cancer, anti-diabetic, and anti-viral agents, and immune stimulants.⁷ The biological potential of this class of compounds has triggered the development of many synthetic methods aiming at the synthesis of these natural products and their analogs.⁶ Since our radical cyclization approach provides an easy entry to the basic skeleton, we decided to advance further to explore the possibility of using this methodology in the synthesis of these polyhydroxylated alkaloids and their analogs.

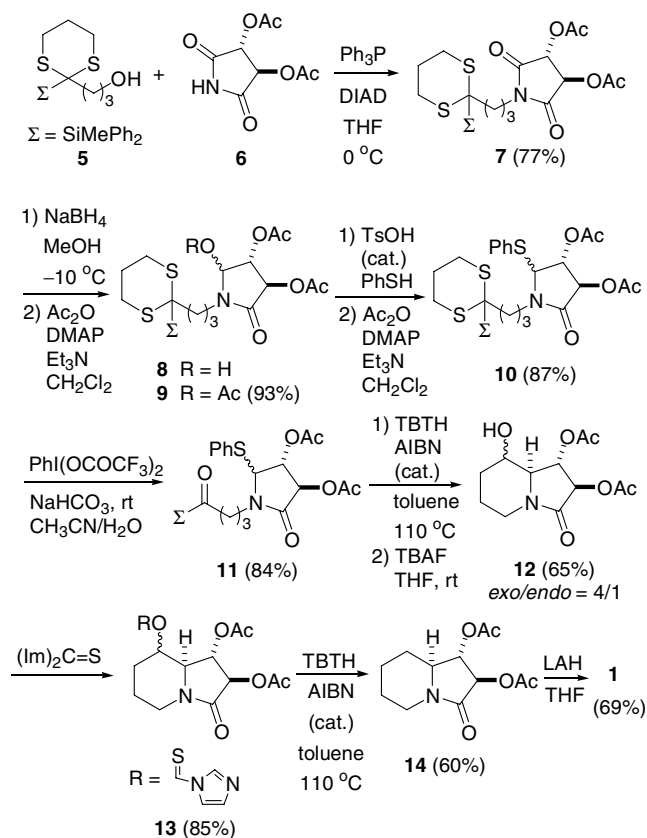


Scheme 2.

2. Results and discussion

As shown in Scheme 3, we started from the chiral template imide **6** derived from L-(+)-tartaric acid.⁸ Mitsunobu coupling⁹ of **6** with alcohol **5**⁵ in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine gave imide **7** in 77% yield. Reduction of **7** with sodium borohydride in methanol¹⁰ afforded carbinol lactam **8**. Attempted exchange of the hydroxyl group with thiophenoxy group under acidic condition met with failure. This is probably due to the difficulty in the generation of an α -acyliminium ion intermediate with two adjacent electron-withdrawing acetoxy groups. We therefore converted the crude carbinol product **8** to triacetate **9** (93%). With a better leaving group, now triacetate **9** can be exchanged successfully with thiophenol in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate.¹⁰ Due to the observation of some acetate hydrolysis, the crude product was reacylated to give sulfide **10** in 87% yield. Hydrolysis of the dithiane moiety with iodobenzene bistrifluoroacetate in wet acetonitrile¹¹ gave acylsilane **11** in 84% yield.

For the key radical cyclization, acylsilane **11** was treated with tributyltin hydride (TBTH) in refluxing toluene in the presence of a catalytic amount of 2,2'-azobisisobutyronitrile (AIBN). The crude product was stirred directly with tetrabutylammonium fluoride (TBAF) in THF to yield 65% of alcohol **12** as an inseparable mixture of *exo*- and *endo*-isomers (*exo/endo* = 4/1). Deoxygenation^{12,13} of the C(8)-hydroxy group was accomplished

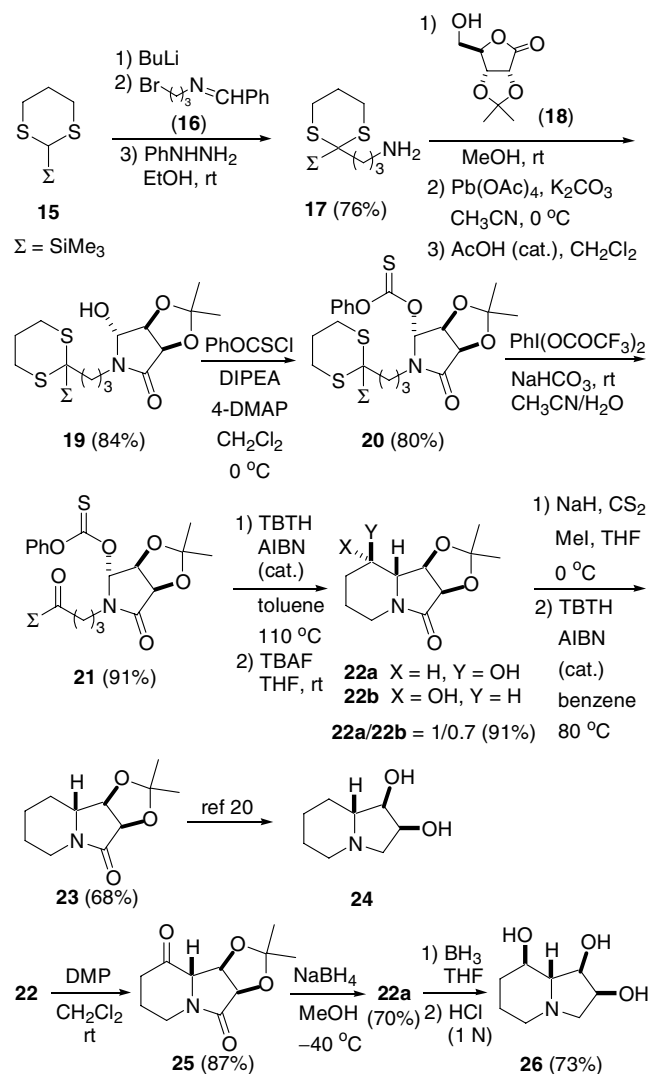


Scheme 3.

by the formation of thiocarbonyl imidazolidine **13** (85%) followed by reduction with TBTH in refluxing toluene to afford diacetate **14** (60%) that is identical spectroscopically to the enantiomer reported in the literature.¹⁴ Further reduction of **14** with LAH gave (+)-lentiginosine (**1**) in 69% yield.¹⁵

The stereochemistry of *exo*-**12** can be identified by comparing with the literature report of its enantiomer.¹⁰ The fact that the Barton deoxygenation process¹² gave a single isomer **14** proved that the other isomer present in **12** was the *endo*-isomer and the stereoselectivity of the cyclization at the bridgehead was excellent.¹⁰ The radical generated from sulfide **11** prefers to attack the acylsilane from the face opposite to the C(4)-acetoxy group as reported by Dener et al.¹⁰

In systems such as 2-*epi*-lentiginosine (**2**) and swainsonine (**3**), the C(1)- and C(2)-hydroxy groups adopt *cis*-relationship. Retrosynthetically the imide approach can be traced back to the non-optimally active *meso*-tartaric acid. We therefore switched to a different chiral template as shown in Scheme 4. Alkylation of 2-trimethylsilyl-1,3-dithiane (**15**) with bromide **16**¹⁶ followed by



Scheme 4.

phenylhydrazine treatment gave us amine **17** in 76% yield.¹⁷ This amine reacted with the commercially available 2,3-isopropylidene-D-ribo-1,4-lactone (**18**), and the resulting crude amide diol was treated with lead tetraacetate followed by acid treatment to afford a single isomer of lactam carbinol **19** in 84% yield over three steps.¹⁸ Exchanging the hydroxyl group in **19** with thiophenol under acidic condition was not successful possibly due to the presence of an acid sensitive isopropylidene protecting group. We therefore took a different approach by converting lactam carbinol **19** to thiocarbonate **20** (80%).¹⁹ Hydrolysis¹¹ of the dithiane moiety as above gave acylsilane **21** in 91% yield. Radical cyclization reaction of **21** followed by desilylation gave an isomeric mixture of alcohols **22** (**22a/22b** = 1/0.7; 91% yield). Barton deoxygenation¹² removed the C(8)-hydroxy group to afford indolizidinone **23** in 68% yield. This material had been converted to (+)-1,8a-di-*epi*-lentiginosine (**24**) by Heitz and Overman.²⁰

Alternatively, alcohols **22** were oxidized with Dess–Martin periodinane (DMP) to yield ketone **25** (87%) as a single isomer. This indicated that the two isomers of **22** were epimeric at C(8). Sodium borohydride reduction of ketone **25** in methanol gave selectively the *exo*-isomer **22a** in 70% yield. Borane reduction of **22a** followed by acid hydrolysis furnished (+)-1,2-di-*epi*-swainsonine^{21,22} (**26**) in 73% yield. This alkaloid is a potent inhibitor of α -D-mannosidase (jack bean) with K_i of 6 μ M.²² Again, the radical cyclization of acylsilane **21** gave very good stereoselectivity at the bridgehead position as in the case of acylsilane **11**. Although the stereochemistry at C(8) is plagued with the lack of stereoselectivity at the hydrogen atom abstraction step of the cyclization reaction, we demonstrated that the orientation of the C(8)-hydroxy group could be manipulated through simple oxidation and reduction processes.

In summary, we have demonstrated that the α -acylamino radical chemistry pioneered by Hart⁴ can be coupled with the acylsilane functionality to produce polyhydroxylated alkaloids in a versatile way. This methodology can well-adopt readily available chiral templates as starting materials. The cyclizations gave excellent stereoselectivity at the bridgehead of the bicyclic structures. Although the stereochemistry of the newly formed silyloxy group cannot be controlled in a highly selective fashion, the stereochemistry can be conveniently manipulated through simple processes. This work also demonstrated that the acylsilane functionality embedded in a complex molecular system can be synthesized and utilized in an useful way.

Acknowledgment

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