行政院國家科學委員會專題研究計畫 成果報告

矽基移位所促進的自由基環化反應研究
研究成果報告(精簡版)

計 畫 類 別 ：個別型
計 畫 編 號 ：NSC 95-2113-M-002-018-
執 行 期 間 ：95 年 08 月 01 日至 96 年 07 月 31 日
執 行 單 位 ：國立臺灣大學化學系暨研究所

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處 理 方 式 ：本計畫可公開查詢

中 華 民 國 96 年 10 月 02 日

行政院國家科學委員會補助專題研究計畫 ■ 成 果 報 告 □期中進度報告

矽基移位所促進的自由基環化反應研究

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中　華　民　國　九十六　年　十　月　二　日

一、中文摘要

我們運用具有掌性的模板合成了幾個具有能產生α-醯胺基自由基之矽基酮，這些矽基酮的自由基環化可以非常有效率的建立一些多羥基的植物鹼，並在形成之雙環橋頭位置具有很好的立體選擇性，這些環化產物進一步的可合成數個天然植物鹼。

關鍵詞：自由基環化、矽基酮、植物鹼

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.

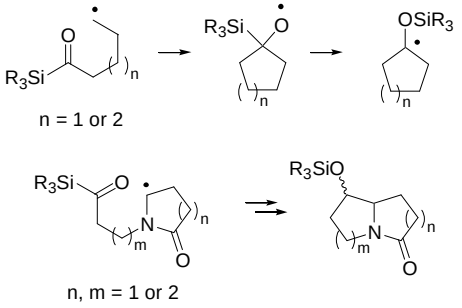
Keywords: Radical cyclizations, Acylsilanes, alkaloids.

二、緣由與目的

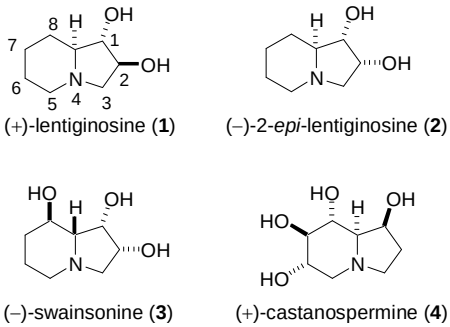
Acylsilanes belong to an interesting class of compounds that displays unusual reactivity.[1] For example, intramolecular radical cyclizations[2] with acylsilanes as the radical acceptors (Scheme 1) proved to be an useful method in the construction of five- and six-membered cyclic alcohols.[3] Several years ago we demonstrated that it was possible to construct silyloxy-substituted pyrrolizidinones, indolizidinones and quinolizidinones via intramolecular cyclizations of α-acylamino radicals[4] with acylsilanes (Scheme 1).[5]

Polyhydroxylated alkaloids[6] (Scheme 2) represented by lentiginosine (**1**),

Scheme 1



Scheme 2



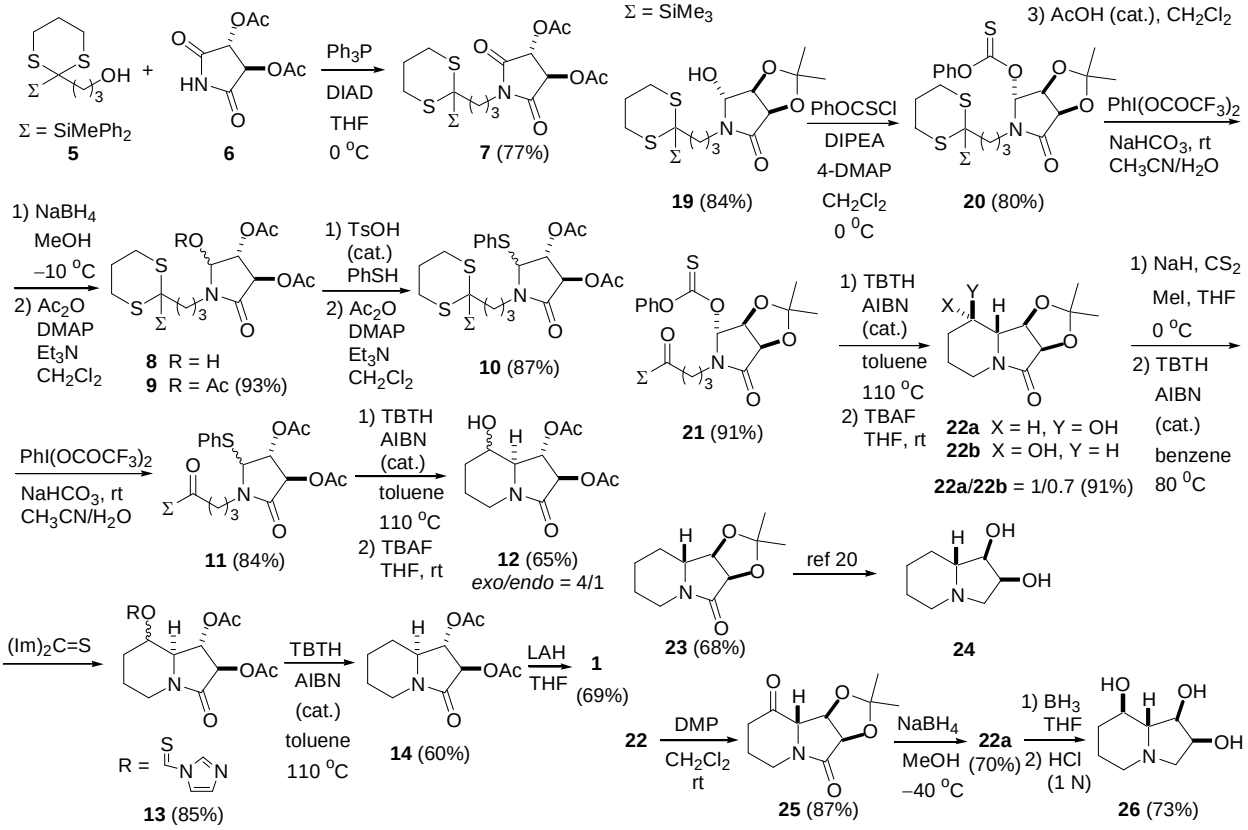
2-*epi*-lentiginosine (**2**), swainsonine (**3**) and castanospermine (**4**) can be potent and selective glycosidase inhibitors and may be useful as anti-cancer, anti-diabetic and anti-viral agents, and immune stimulants.[7] The biological potential of this class of compounds has triggered the development 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.

三、研究報告應含的內容

As shown in Scheme 3, we started from the chiral template imide **6** derived from L-(+)-tartaric acid.[8] Mitsunobu coupling[9] 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 methanol[10] 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 reacetylated to give sulfide **10** in 87% yield. Hydrolysis of the dithiane moiety with iodobenzene bistrifluoroacetate in wet acetonitrile[11] gave acylsilane **11** in 84% yield.

Scheme 3



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 by the formation of thiocarbonyl imidazolide **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]

Scheme 4

The stereochemistry of *exo*-**12** can be identified by comparing with the literature report of its enantiomer.[10] The fact that the Barton deoxygenation process[12] 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, Hart and Ramesh.[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 would trace back to the non-optically 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 phenylhydrazine treatment gave us amine **17** in 76% yield.[17] This amine reacted with the commercially available 2,3-isopropylidene-D-ribono-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] Hydrolysis[11] 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 deoxygenation[12] 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 μM.[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 Hart[4] 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 can not 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.

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