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Original article

Rapid construction of the unique BCD ring system of tricyclo[6.2.1.0] undecane in the C_{19}-diterpenoid alkaloid aconitine

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ABSTRACT

A model study leading to the preparation of the unique tricyclo [6.2.1.0] undecane BCD ring systems of aconitine is described. The synthesis features an unprecedented diastereoselective oxidative dearomatization/dimerization/retro-DA/IMDA cascade reaction and a highly efficient Wagner-Meerwein rearrangement.

1. Introduction

C_{19}-Diterpenoid alkaloids are a large family of highly complex polycyclic alkaloids, which are characterized by an intricate hexacyclic ring system, heavily substituted by a series of oxygen functions such as hydroxy, methoxy and acyloxy groups (Fig. 1) [1]. More than 600 family members have been isolated over the past 60 years. A survey of an extensive number of these alkaloids reveals anti-arrhythmic, anti-inflammatory, anti-epileptic, hypotensive, and bradycardic properties. This broad spectrum of biological activity can be attributed to the potent interactions of these alkaloids with voltage-dependent sodium, potassium, and calcium ion channels [2]. While the toxicity of the most of active compounds has so far limited their clinical application, less toxic derivatives are emerging that could prove to be promising drug candidates [3].

The structural intricacy and biological significance of C_{19}-diterpenoid alkaloids have attracted the great attention of many synthetic chemists over the last fifty decades. Early important and impressive contributions to the syntheses of the C_{19}-diterpenoid alkaloids including a synthesis of talatizamine **1**, chasmanine **2**, and 13-desoxydephonine **3** were made by Wiesner and coworkers in 1970's [4]. Recently, an elegant synthesis of neofinaconitine **4** was completed by the group of Gin using a highly convergent strategy [5]. Subsequently, Sarpong's group and Fukayama's group reported the total syntheses of liljestrandinine **6** and weisaconitine D **5** [6] and the first asymmetric total synthesis of (−)-cardiopetaline **7** [7] respectively, both of which employ a late-staged Wagner−Meerwein rearrangement from a C_{20}-DA skeleton as the key transformation. Despite numerous other synthetic efforts [8,9], these compounds **1-7** remain the only seven natural C_{19}-diterpenoid alkaloid molecules completed by total syntheses to date. Some C_{19}-diterpenoid alkaloids with more complex oxygen functions and distinguished biological activities, *e.g.*, aconitine **8** and methyllycaconitine, are still the highly attractive and challenging targets for total synthesis.

In view of our long-standing interest toward the chemistry of C_{19}-diterpenoid alkaloids with significant biological activities [9], we planned to initiate a new program to study the total synthesis of aconitine **8**. To achieve this goal, we conceived that it was necessary to develop an efficient and scalable synthesis for the rapid construction of the unique tricyclic subunit of tricyclo [6.2.1.0] undecane core **12**. Our whole synthetic plan based on this tricyclic skeleton is briefly outlined in Scheme 1, We envisioned that aconitine **8** can be firstly transformed to intermeidate **9** by means of a serials of functional groups interconversions. Then disconnections of C4-C5 and C3-C4 bond involving sequential 6-*exo-trig* radical cyclization [10] and Michael addition could greatly simplify the hexacyclic molecule into the less complicated

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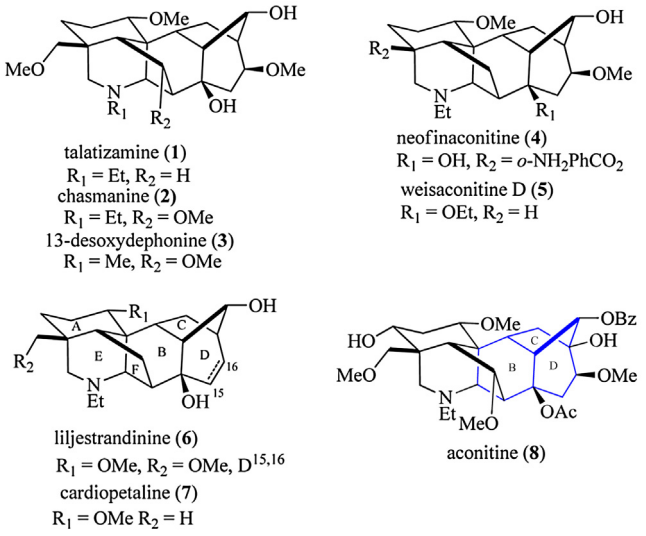
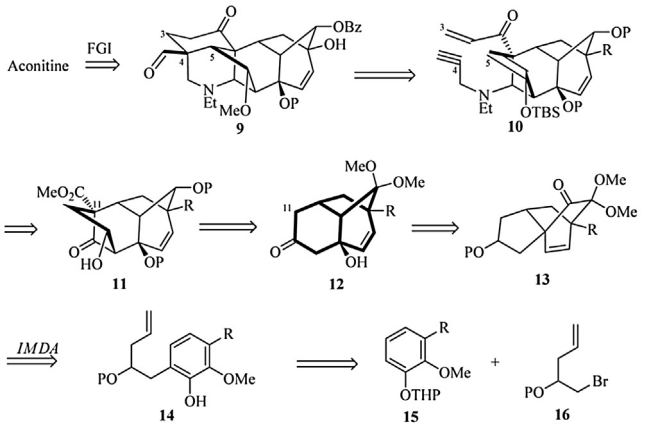


Fig. 1. Structures of C_{19}-diterpenoid alkaloids.



Scheme 1. Retrosynthetic analysis of aconitine.

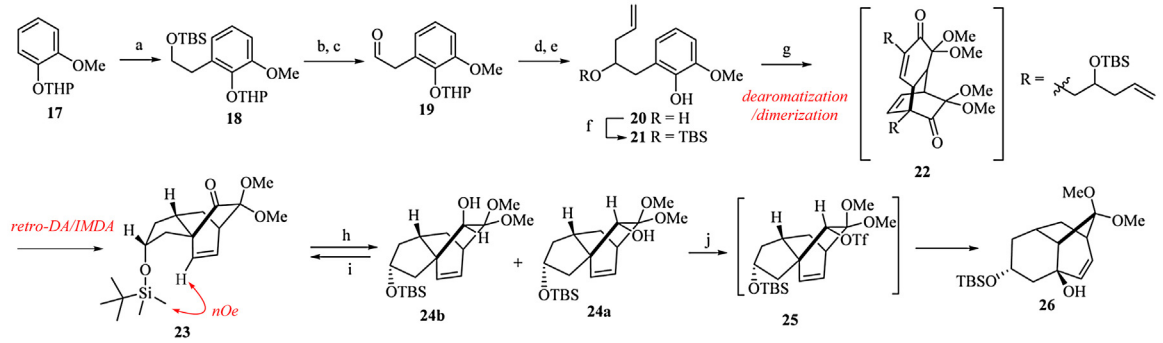
tetracyclic structure **10**, which might be further degraded into structure **11**. With a successive alkylation and intramolecular aldol reaction strategy [11], **11** could be generated from **12** by installation of the five-membered ring F on ring B. Thus, development of a highly efficient synthetic route to access this tricyclic intermediate **12** is fairly crucial to realize our whole synthetic strategy.

Herein, we wish to report a short sequence to prepare this key tricyclic skeleton using an unprecedented oxidative dearomatization/dimerization/retro-DA/IMDA cascade reaction and Wagner-Meerwein rearrangement as the key steps.

2. Results and discussion

As illustrated in Scheme 2, we began our synthetic study with the preparation of the phenol **21** tethering an oxygen substituted olefinic side chain. Thus, coupling **17** with the iodide derivative in presence of *n*-butyl lithium provided the **18**. Removal of TBS protecting group followed by oxidation of primary alcohol with Dess-Martin periodinane afforded the aldehyde **19** in 90% yield. Barbier's allylation [12] of aldehyde **19** with allyl bromide in the presence of Zn/NH_4Cl followed by removal of the THP group under acidic condition furnished the allylic alcohol **20**. Finally, selective protection of allylic alcohol with TBS provided the phenol **21**, ready for the next crucial oxidative dearomatization/intramolecular Diels-Alder (IMDA) cascade reaction. Initial execution of phenol **21** to the oxidative condition by treatment with diacetoxyiodobenzene (PIDA) in a diluted methanonic solution at reflux gave the desired cycloadduct **23** as minor product while the intermolecular Diels-Alder cycloadduct dimer **22** as the major product [9b]. Gratifyingly, we next found this dimer **22** could be successfully converted to the cycloadduct **23** in excellent yield through a retro-DA/IMDA process under a thermodynamic condition (heating at 180 °C in mesitylene) [13]. Thus, a cascade process involving oxidative dearomatization/dimerization/retro-DA/IMDA reaction could be actually applied to this transformation in one pot. Upon complete formation of dimer **22** by exposure of **21** to PIDA in methanol at low temperature, simply switch the solvent to mesitylene followed by heating at 180 °C directly led to the desired cycloadduct **22** in excellent yield and fairly good diastereoselectivity. The stereochemistry of **22** was assigned on the basis of the established *endo* cycloaddition mechanism [13a] as well as the observed NOE correlation between the methyl of TBS group and the olefin proton. It is worthwhile to mention that the high diastereoselectivity of this reaction make it possible to realize enantioselective synthesis of this important intermediate, as long as construction of the asymmetric chiral center of the secondary alcohol **20**.

With the requisite tricycle functionality in place, the deformation of the [2.2.2]octane subunit of **23** to the [3.2.1] subunit by means of the Wagner-Meerwein rearrangment was addressed next. To realize this desired transformation, it is requisite to reduce



Scheme 2. Synthesis of BCD ring system **26**. Reagents and conditions: (a) *n*-BuLi, THF, 0 °C–r.t., 2 h, 82%; (b) TBAF, THF, r.t., 30 min, 97%; (c) DMP, $NaHCO_3$, DCM, r.t., 30 min, 90%; (d) allyl bromide, zinc powder, THF/sat. aq NH_4Cl (1:4 v/v), r.t., 30 min; (e) 3 mol/L aqueous HCl, MeOH, r.t., 1 h, 87% over two steps; (f) TBSOTf, 2,6-lutidine, DCM, 0 °C, 1 h, 80%; (g) PIDA, MeOH, 0 °C–r.t., 4 h, then mesitylene, 180 °C, 4 h, 90%; (h) $LiAlH_4$, THF, 0 °C, 3 h, 40% for **24b** and 50% for **24a**; (i) oxalyl chloride, DMSO, Et_3N, DCM, −78 °C – −30 °C, 1 h, 94%; (j) Tf_2O, pyridine, DCM, 0 °C, 1 h then silica gel, 85%.

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