Tetrahedron 73 (2017) 4201–4205

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An unexpected aziridination/rearrangement/oxidation tandem reaction leading to the total synthesis of (−)-mersicarpine

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ARTICLE INFO

Article history:
Received 17 August 2016
Received in revised form
17 November 2016
Accepted 18 November 2016
Available online 19 November 2016

Keywords:
Total synthesis
Indole alkaloids
Mersicarpine
Cycloaddition
Rearrangement

ABSTRACT

With the aim to synthesize anti-mitotic natural product (−)-rhazinal, we proposed a strategy based on a dearomative intramolecular [3+2] cycloaddition between alkyl azide and indole, followed by rearrangement to furnish the featured tetracyclic framework. During the reaction condition screening, we accidentally encountered a tandem [3+2] cycloaddition/rearrangement/oxidation reaction, which enabled the synthesis of another alkaloid, (−)-mersicarpine, in four steps with 35% overall yield from a reported intermediate. The tandem [3+2] cycloaddition/rearrangement reaction disclosed herein could provide a method for the synthesis of other structurally intriguing alkaloids.

1. Introduction

Monoterpene indole alkaloids constitute an important family of natural products with significant biological activities, which have demonstrated utility as anti-cancer, anti-malarial and anti-arrhythmic agents.[1] Biosynthetically, these diverse small molecules derived from the combination of tryptamine and a C9 or C10 fragment originating from secologanin.[1] Based on the different structures of C9 or C10 fragments, subfamilies of monoterpenoid indole alkaloids have been discerned, such as *corynanthe*, *iboga* and *aspidosperma* classes.[2] We have recently reported a novel synthesis of *iboga* alkaloids, which also led to the efficient preparation of vinblastine, an anti-microtubule agent widely used in both clinical and basic research.[3] As a matter of fact, (−)-rhazinal (**1**, Fig. 1) and its congener (−)-rhazinilam (**2**) have also been reported to interfere with microtubule dynamics in vitro and exhibit cytotoxicity towards various cancer cell lines at low micromolar range.[4] First isolated from the stem-bark extract of *Kopsia* species,[5] (−)-rhazinal (**1**) contains a strained nine-membered lactam ring fused to a tetrahydroindolizine skeleton and bears a quaternary carbon linked to the C2-position of pyrrole. Besides **1** and **2**, a series of *aspidosperma* alkaloids such as mersicarpine (**3**), secoleuconoxine, and leuconoxine were isolated from the *Kopsia* species of flowering plants,[6] which is presumed to have biogenetic relations.[7]

Due to the unusual structure as well as intriguing biological activity, rhazinal (**1**) and rhazinilam (**2**) have attracted wide attention from the synthetic chemistry community, providing a platform to demonstrate novel methodologies. Furthermore, recent divergent syntheses of representative *aspidosperma* alkaloids not only accomplished rhazinilam (**2**) as one of the targets but illustrated their structural relation as well.[8] Strategically, most syntheses of rhazinal (**1**) or rhazinilam (**2**) depended on a sequence of constructing the tetrahydroindolizine ring system followed by the final installment of the nine-membered lactam.[8,9] One exception was to establish the tetrahydroindolizine and nine-membered lactam in one step via an elegant transannular cyclization, which was reported by Zakarian group in 2010.[10]

Keen on using rearrangement reactions to facilitate the synthesis of biologically important natural products,[3,11] we proposed a new approach (Fig. 2) to (−)-rhazinal (**1**) in order to further the associated chemical biology studies. However, during the investigation of this synthetic plan, we serendipitously obtained (−)-mersicarpine (**3**), another interesting alkaloid that has also

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http://dx.doi.org/10.1016/j.tet.2016.11.049
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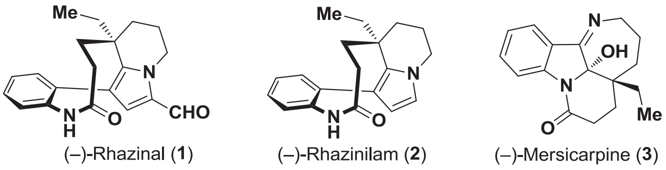


Fig. 1. *Aspidosperma* alkaloids discussed in this report.

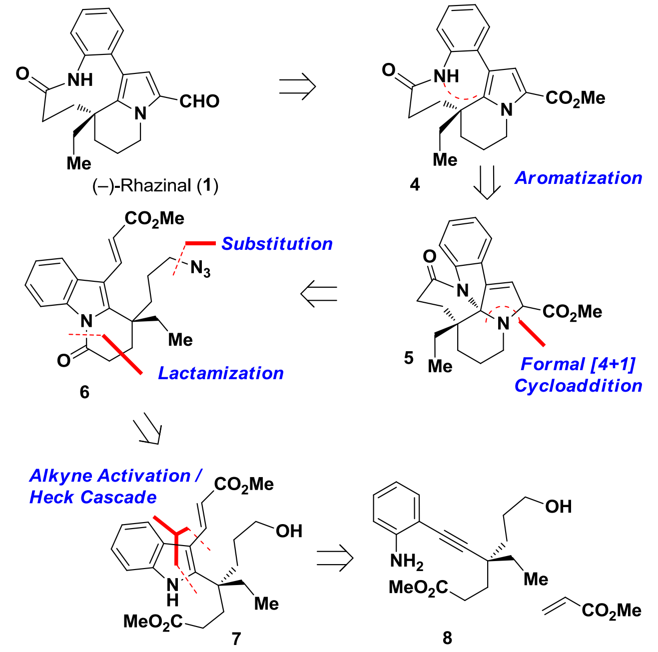
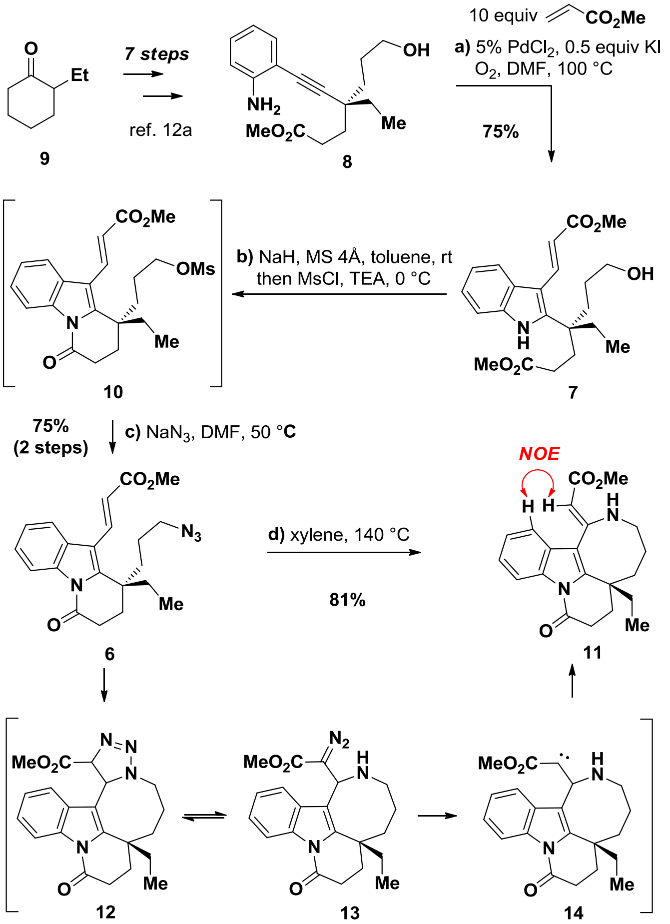


Fig. 2. Retrosynthetic analysis of (−)-rhazinal (**1**) based on the formal [4+1] cycloaddition followed by C–N bond scission.



Scheme 1. Attempted approach towards (−)-rhazinal (**1**).

been widely appreciated as the target for total synthesis.[7b,8c,12] Herein, we detail our discovery of the unexpected tandem process leading to this indole alkaloid.

2. Results and discussion

We envisioned the pyrrole ring and nine-membered lactam of (−)-rhazinal (**1**) could be constructed in the final stage by a tandem process involving cycloaddition and fragmentation (Fig. 2). Specifically, intermediate **4** could be afforded by the scission of one C–N bond in pentacyclic compound **5** driven by the aromatization into a pyrrole. The fused dihydropyrrole ring system in **5** could be formed by the intramolecular formal [4+1] cycloaddition of azidodienes developed by the groups of Hudlicky and Pearson,[13] which involved the sequence of intramolecular azide-alkene 1,3-diplor cycloaddition, nitrogen extrusion,[14] and vinylaziridine ring-expansion.[15] Admittedly, this desired transformation in our scenario would be a challenging one and azide has not been employed in the dearomative annulation of substituted indoles.[16] Azide **6** could be derived from alcohol **7** via lactamization and substitution manipulations. We planned to construct the substituted indole in **7** from alkynylaniline **8**, a known compound,[12a] using a Pd-catalyzed heterocyclization/oxidative Heck coupling.[17]

Starting from commercially available cyclohexanone **9** (Scheme 1), we first prepared enantiopure **8** bearing the desired quaternary stereogenic center following the seven-step sequence reported by the Fukuyama group.[12a] After some optimization (see Table S1 in Supporting Information for details), the $PdCl_2$-KI catalytic system using oxygen as the oxidant successfully converted alkynylaniline **8** to indole **7** in 75% yield. Sequential lactam formation followed by mesylation of the primary alcohol provided the corresponding **10**, and the crude mesylate **10** was converted to **6** directly upon treatment with sodium azide. With the precursor of the key cycloaddition/rearrangement tandem process in hand, we first investigated the thermal conditions. When **6** was heated at reflux in xylene, product **11** was isolated as the only product in 81% yield, where the geometry of olefin was assigned by NOESY experiment. This result suggested the [3+2] reaction took place between the azide and the double bond conjugated to indole to give triazoline **12** at first, which could isomerize to diazoester **13** and generate carbene **14** at high temperature, while the 1,2-hydrogen shift of **14** eventually generated **11** (see Fig. S1 in Supporting Information for another possible mechanism).[18] The aromaticity of indole and steric factors could rationalize the preference of the azide to react with the exocyclic double bond, leading to a strained 8-membered ring. In contrast, most of the reported examples of intramolecular 1,3-dipolar cycloaddition of azide to olefin were dominated by the formation of 5-membered or 6-membered tethered rings.[13,18,19] To our knowledge, only one example has been reported that constructed an 8-membered ring.[20]

Other reaction conditions were also evaluated in order to enable our desired transformation on substrate **6**. Lewis acids have been reported to mediate not only the cycloaddition of alkyl azides and enones but also the rearrangement of resulting triazoline