Tetrahedron 68 (2012) 6249–6256

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

# Novel skeletal rearrangements of a diterpene derived from deltaline

Pei Tang, Ling Wang, Qi-Feng Chen, Qiao-Hong Chen, Xi-Xian Jian, Feng-Peng Wang *

*Department of Chemistry of Medicinal Natural Products, West China College of Pharmacy, Sichuan University, No. 17, Duan 3, Renmin Nan Road, Chengdu 610041, PR China*

ARTICLE INFO

*Article history:*
Received 24 March 2012
Received in revised form 5 May 2012
Accepted 15 May 2012
Available online 23 May 2012

*Keywords:*
$C_{19}$-Diterpenoid alkaloid
Diterpene
Rearrangement
Deltaline

ABSTRACT

Treatment of imines **5** and **7**, both prepared from the $C_{19}$-diterpenoid alkaloid deltaline (**1**), with $NaNO_2$–HCl resulted in the formation of diterpene **6** with an eight-membered ring through a sequence of denitrogenation and enlargement of ring B. In addition, two unusual skeletal rearrangements of diterpene **6** were also observed, leading to two structurally novel products **8** and **10**. The structures of compounds **8** and **10** were confirmed by their X-ray crystallographic analyses and 2D NMR data.



## 1. Introduction

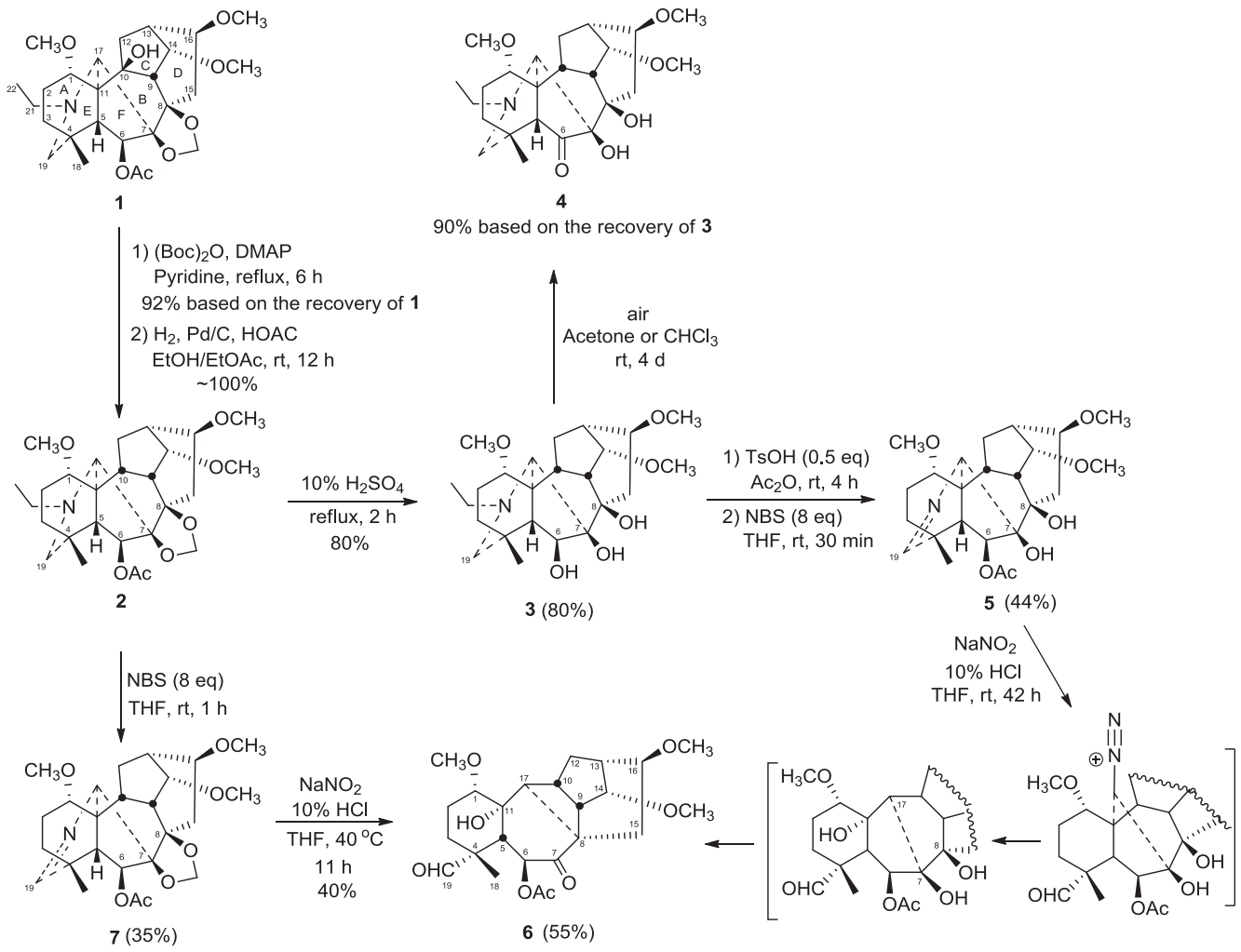
The diterpenoid alkaloids are a group of structurally complex natural products, displaying various pharmacological activities[1a–d,4] and intriguing chemistry.[1d–e] The diterpenoid alkaloids have mainly been isolated from the plants of genera *Aconitum* and *Delphinium* (Ranunculaceae), and *Spiraea* (Rosaceae).[1–3] The diterpenoid alkaloids have attracted lasting attention from our research group due to the unique architecture and interesting reactions.[1d] During the course of this investigation, we have observed an interesting skeletal rearrangement when treating imine analogs of aconitine-type $C_{19}$-diterpenoid alkaloids with $HNO_2$, leading to diterpenes with an eight-membered ring.[5,6] This kind of rearrangement underwent a sequence of denitrogenation and ring enlargement, which inspired us to apply the rearrangement, as a key reaction, to the conversion of the lycoctonine-type $C_{19}$-diterpenoid alkaloid deltaline (**1**) to taxanes. The ring enlargement and denitrogenation of deltaline (**1**), and unprecedented skeletal rearrangements of the diterpene **6** are herein described.

## 2. Results and discussion

We have successfully achieved an efficient synthesis of taxane ABC core system from deltaline (**1**).[7] We have envisioned a new strategy toward the conversion from deltaline (**1**) to taxanes, in which the eight-membered ring was planned to introduce by a sequence of denitrogenation and ring enlargement. This study was started with the preparation of deltaline imine analog. To avoid the troublesome that 10-OH might cause, 10-deoxydeltaline (**2**) was prepared by refluxing **1** with $Boc_2O$ and DMAP in pyridine[8] followed by hydrogenation of the resulting $\Delta^{10\ (12)}$ olefin (Scheme 1). The dioxymethylene moiety in compound **2** was smoothly converted to a diol unit in compound **3** by refluxing with 10% $H_2SO_4$ for 2 h. Ketone **4** was observed when a solution of triol **3** in acetone or chloroform was kept standing at room temperature for 4 days, suggesting that 6-OH in triol **3** is readily oxidized. To avoid this kind of undesired transformation, the secondary hydroxyl group at C-6 in triol **3** was selectively protected as acetate. The acetate was then converted to the corresponding imine **5** in 44% yield employing the method developed by us.[9–12] The HR-ESIMS of **5** exhibited a quasimolecular ion peak at *m*/*z* 450.2498 $[M+H]^+$, corresponding to the molecular formula $C_{24}H_{35}NO_7$. The NMR ($^1H$ and $^{13}C$) showed the characteristic imine signals at $\delta_C$ 169.7 (d) and at $\delta_H$ 7.43 (1H, br s). We optimized ring enlargement reaction by treating imine **5**, possessing two vicinal tertiary hydroxyl groups, with $HNO_2$ generated in situ from $NaNO_2$–HCl, to give diterpene **6** in 55% yield (Scheme 1). The molecular formula of compound **6** was established as $C_{24}H_{34}O_8$ and its structure was established as drawn in Scheme 1 according to the pseudomolecular ion peak at *m*/*z* 473.2145 $[M+Na]^+$ in the HR-ESIMS and NMR ($^1H$ and $^{13}C$) data. Formation of diterpene **6** from the diterpenoid alkaloid **5** was through a sequence including denitrogenation, enlargement of ring B, and Pinacol rearrangement. We next investigated the ring enlargement reaction on an imine substrate with a dioxymethlene moiety. The imine **7** was smoothly prepared by treating compound **2** with NBS in 35% yield. Gratifyingly, when

* Corresponding author. Tel./fax: +86 28 85501368; e-mail address: wfp@scu.edu.cn (F.-P. Wang).

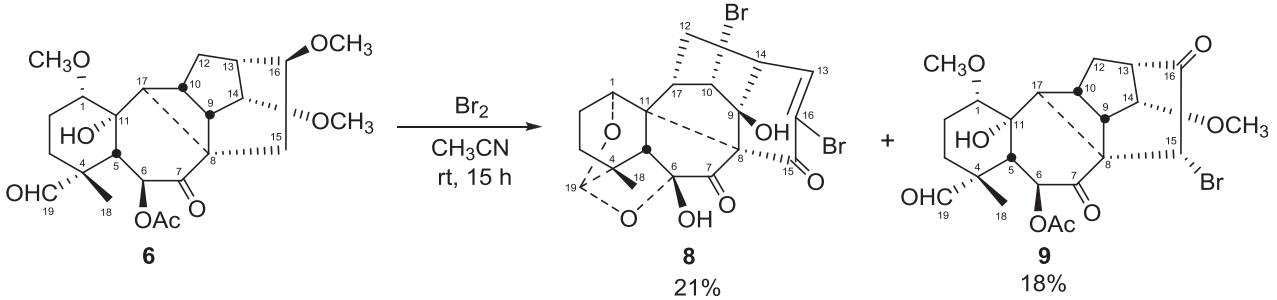
0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.05.058




**Scheme 1.**

imine **7**, having a dioxymethylene moiety, was subjected to the ring enlargement reaction conditions mentioned above at 40 °C, the ketone **6** was obtained as well through a sequence of ring enlargement, cleavage of methylene from the dioxymethylene moiety, and Pinacol rearrangement. Consequently, ring enlargement product **6** can be prepared from lycoctonine-type diterpenoid alkaloid **2**, having a hydroxyl group at C-7, by two protocols with a four-step and two-step sequence, respectively (Scheme 1).

As a key intermediate to taxanes, compound **6** has a drawback because it contains a [6+4] ring system instead of a pure eight-membered ring. To convert compound **6** as an efficient intermediate in our conversional synthesis of taxanes, its C(8)–C(17) bond should be broken. We have found that a four-membered ring next to a ketone carbonyl group can be attacked by a halide, leading to the opening of the four-membered ring.[13] We next attempted to apply this method to the opening of the four-membered ring in compound **6**. Heating compound **6** with bromine resulted in a messy crude product; while treatment of **6** with bromine in acetonitrile at room temperature for 15 h followed by column chromatography furnished dibromide **8** in 21% yield and ketone **9** in 18% yield (Scheme 2). The HR-ESIMS of **8** exhibited three pseudomolecular ion peaks at *m*/*z* 522.9382, 524.9332, and 526.9315 $[M+Na]^+$ in about a 1:2:1 ratio, characteristic of a dibromo compound. The molecular formula of **8** was established as $C_{19}H_{18}O_6Br_2$ on the basis of its HR-ESIMS and NMR data. The NMR data of **8** ($^1H$, $^{13}C$, and HMQC, Table 2), which are significantly different from




**Scheme 2.**