Chinese Chemical Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Chinese Chemical Letters

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

Original article

An alternative total synthesis of bolivianine

Jin-Peng Li, Chang-Chun Yuan, Biao Du, Bo Liu *

Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China

ARTICLE INFO

Article history:
Received 28 April 2016
Received in revised form 19 May 2016
Accepted 25 May 2016
Available online xxx

Keywords:
Total synthesis
Cyclopropanation
Aldol
Diels-Alder
Terpenoid

ABSTRACT

An alternative total synthesis of bolivianine in twelve steps is herein reported on the basis of our previous successful bioinspired total synthesis. The present total synthesis features straightforward transformation from an aldol product to the butenolide of the target molecule, and stereoselective Diels-Alder cycloaddition to construct ring E, as well as the final spontaneous IMHDA process.

1. Introduction

Bolivianine is a structurally intriguing sesterterpenoid as shown in Fig. 1, isolated from *Hedyosmum angustifolium* (Chloranthaceae) by the Jullian group in 2007 [1]. Although no bioactivity of this sesterterpenoid was reported, we were attracted by its structural complexity and synthetic challenge. In 2013, our group reported the first and bioinspired asymmetric total synthesis of bolivianine with commercially available (+)-verbenone as the starting material [2]. Led by our biogenetic hypothesis, this total synthesis features efficient assembly of a 3/5/6 architecture through intramolecular cycloprop anation of an allylic metal carbene intermediate [3], and an ambitious Diels-Alder/intramolecular hetero-Diels-Alder (DA/IMHDA) cascade to install the EFG tricycle of bolivianine in one pot [4].

In our previous bioinspired total synthesis of bolivianine as illustrated in Scheme 1 [2,4], compound **3** was prepared from (+)-verbenone in seven steps. Aldol reaction with compound **4** and subsequent acidic treatment transformed **3** to the furan **5** in one pot. DIBAL-H reduction and silyl protection afforded compound **6**, which was elaborated after oxidative dearomatization and silyl deprotection to produce onoseriolide **7**, a natural sesquiterpenoid [5]. Final IBX oxidation and biomimetic DA/IMHDA cascade with the monoterpene **9** [6] furnished bolivianine in 14 steps. Actually, we were unsatisfied with the synthetic procedure from compound **3** to the target molecule since it is not concise enough. Herein we report our efforts on the promotion of our previous total synthesis.

2. Experimental

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dichloromethane (DCM), diisopropylamine (DIPA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and toluene were distilled from calcium hydride under argon. Tetrahydrofuran was distilled from sodium-benzophenone. All the chemicals were purchased commercially and used without further purification, unless otherwise stated. Flash chromatography was performed using silica gel (200–400 mesh). Reactions were monitored by thin layer chromatography (TLC). Visualization was achieved under a UV lamp (254 nm and 365 nm), I_2 and by developing the plates with p-anisaldehyde or phosphomolybdic acid. NMR were recorded on Bruker DRX-400 MHz NMR spectrometer with TMS as the internal standard and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: ^1H NMR = 7.26, ^{13}C NMR = 77.16; C_6D_6: ^1H NMR = 7.28, ^{13}C NMR = 127.82). Coupling constants (J) are reported in Hertz (Hz). Optical rotations were measured at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]_D^T$, concentration (g/100 mL), and solvent. High resolution Mass spectra (HRMS) were recorded by using FTMS-7 spectrometers. Infrared spectra (IR) were recorded on a NEXUS 670 Fourier transform infrared spectrophotometer and are reported in wavenumbers (cm^{-1}).

* Corresponding author. Tel.: +86 28 8541 3712; fax: +86 28 8541 3712.
E-mail address: chembliu@scu.edu.cn (B. Liu).

http://dx.doi.org/10.1016/j.cclet.2016.06.013

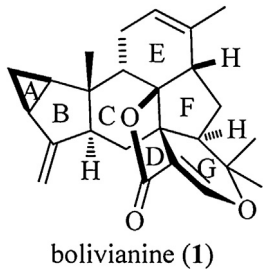
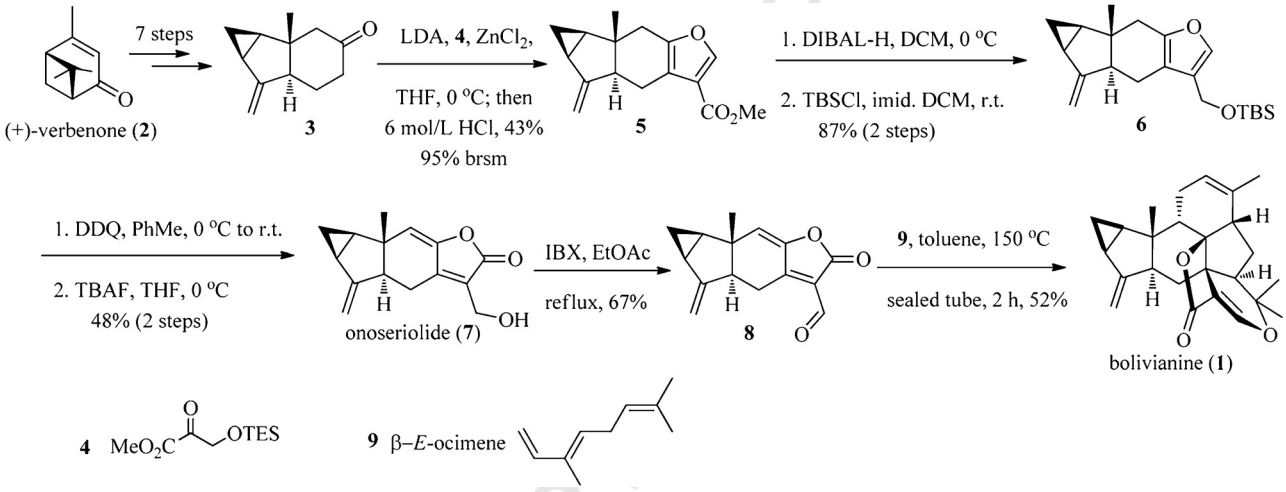


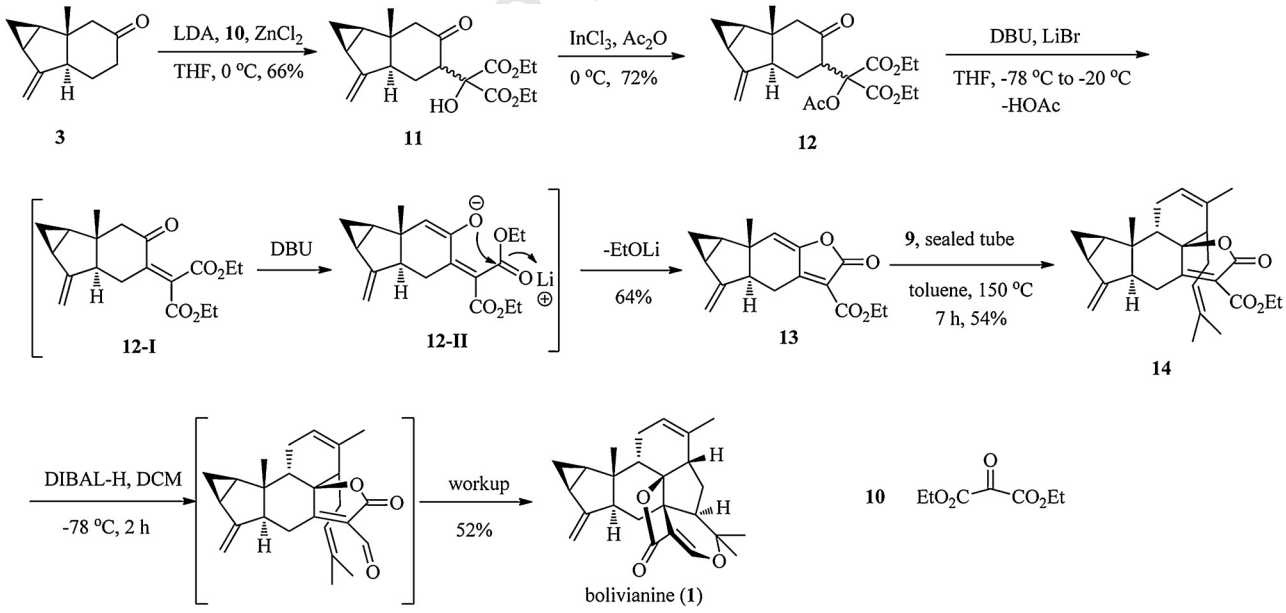
Fig. 1. Molecular structures of bolivianine.

Preparation of compound **11** (Scheme 2): To a stirred solution of lithium diisopropylamide (LDA), prepared from diisopropylamine (DIPA) (534.3 mg, 0.75 mL, 5.28 mmol) and *n*-BuLi (2.5 mol/L in hexane, 2.11 mL, 5.28 mmol) in THF (20 mL), was added a solution of **3** (374.3 mg, 2.11 mmol) in THF (5 mL) at 0 °C. After the resulting mixture was stirred for 30 min at the same temperature, the mixture of diethyl ketomalonate **10** (919.5 mg, 0.81 mL, 5.28 mmol) and $ZnCl_2$ (719.6 mg, 5.28 mmol) in THF (15 mL) was added dropwise to the above solution at 0 °C. After stirring for another 1 h at 0 °C, the resulting mixture was quenched with saturated NH_4Cl solution (20 mL). The layers were separeted and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (6:1 petroleum ether/EtOAc) to give compound **11** (488.0 mg, 66%) as a colorless oil.

Preparation of compound **12**: To a stirred solution of **11** (112.5 mg, 0.32 mmol) in acetic anhydride (0.3 mL) was added $InCl_3$ (7.1 mg, 0.03 mmol) in acetic anhydride (0.7 mL) slowly at 0 °C. The resulting mixture was stirred for 15 min at this temperature. The reaction was quenched with saturated $NaHCO_3$ solution (60 mL), and the resulting mixture was stirred over night at 0 °C. The layers were seperated and the auqeous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (4:1 petroleum ether/EtOAc) to give compound **12** (85.4 mg, 72%) as a light yellow oil.



Scheme 1. Our previously published bioinspired total synthesis of bolivianine (**1**).



Scheme 2. The promoted total synthesis of bolivianine.

Please cite this article in press as: J.-P. Li, et al., An alternative total synthesis of bolivianine, Chin. Chem. Lett. (2016), http://dx.doi.org/10.1016/j.cclet.2016.06.013