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Enantioselective total synthesis of virosaine A and bubbialidine†‡

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Hideki Miyatake-Ondozabal, Linda M. Bannwart and Karl Gademann*

The first enantioselective total syntheses of virosaine A and bubbialidine are described. Key transformations include the formation of a tetracyclic intermediate *via* an intramolecular aza-Michael addition, generation of a *N*-hydroxy-pyrrolidine through a Cope elimination and an intramolecular [1,3]-dipolar cycloaddition to generate a complex 7-oxa-1-azabicyclo[3.2.1]octane ring system.

The securinega alkaloids are a family of bridged tetracyclic natural products occurring in the plants of the *Securinega*, *Phyllanthus*, *Flueggea* and other genera in the Euphorbiaceae family.[1] Recently, two new birdcage-shaped alkaloids with unprecedented skeletal structures were isolated, namely virosaine A (**1**) and virosaine B (**2**), from the twigs and leaves of *Flueggea virosa* (Fig. 1).[2] The unique structural features of these pseudoenantiomers are characterized by their densely functionalized, stereochemically complex architecture featuring an unusual tetracyclic core incorporating a trihydro-1,2-oxazine ring. Neither **1** nor **2** showed cytotoxic activity against selected cancer cell lines (MCF-7, MDA-MB-231, HepG2, HepG2/ADM, HL-60, K562 and Hep2).[2]

Among this family of natural products, securinine (**3**) is the most abundant and widely spread alkaloid possessing an impressive range of biological activity including neurotransmitter gamma-aminobutyric acid (GABA) receptor antagonism,[3] *in vivo* CNS activity and anti-malarial and anti-bacterial activities.[4,5] Due to its remarkable biological activities and intriguing molecular structure, numerous total syntheses have been reported to date.[1b,6] Conversely, a related yet much rarer securinega alkaloid (+)-phyllantidine (**4**) has a similar cyclic hydroxylamine scaffold to virosaines A (**1**) and B (**2**) and only one total synthesis has been published due to its complex architecture.[7] During the preparation of this manuscript, the first total synthesis of virosaine B was reported by Yang, Li and coworkers.[8] Two other putatively related

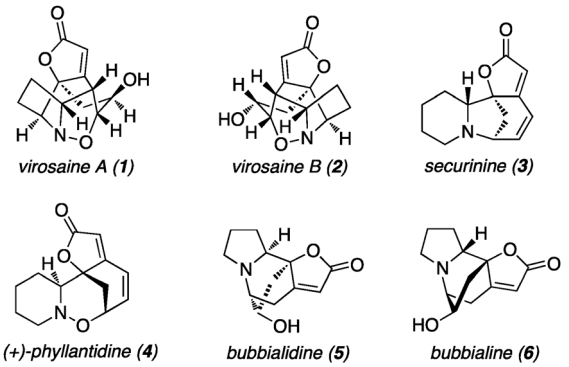


Fig. 1 Virosaines A, B and examples of related alkaloids.

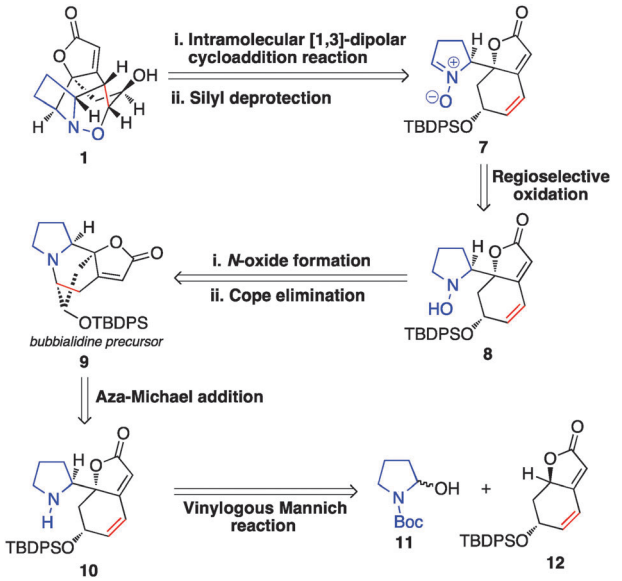
alkaloids bubbialidine (**5**) and bubbialine (**6**) were isolated from the leaves of *Zygogynum pauciflorum* by Potier *et al.* in 1990.[9] There is no reported publication for the synthesis of virosaine A and bubbialidine to date. In this communication, we report the first total syntheses of virosaine A (**1**) and bubbialidine (**5**).

Our brief retrosynthetic analysis is illustrated in Scheme 1. The main synthetic strategies are the vinylogous Mannich reaction, an intramolecular aza-Michael addition, a late-stage regioselective oxidation of the pyrrolidine moiety to the nitrone and the subsequent intramolecular [1,3]-dipolar cycloaddition. Inspired by the proposed biosynthesis of virosaines suggested by Zhang, Ye and coworkers,[2] we envisaged that nitrone **7** should undergo a stereoselective intramolecular cycloaddition to form the complex tetracyclic core **1**, creating three new stereogenic centres. A regioselective oxidation could be achieved in *N*-hydroxy-pyrrolidine **8** leading to **7**. Following a synthetic strategy described by Magnus *et al.*,[10] oxidation precursor **8** should be available from tetracycle **9** through an *N*-oxidation–Cope elimination sequence. An intramolecular aza-Michael addition of pyrrolidinyl-furanone **10** would allow the formation of **9**, which will serve as a masked alkene intermediate enabling *N*-oxidation in the next step. Finally, a vinylogous Mannich reaction between aminol **11** and furanone **12** should provide the key intermediate **10** after *t*-butyloxycarbonyl (Boc) deprotection.

Department of Chemistry, University of Basel, St. Johanns-Ring 19, Basel 4056, Switzerland. E-mail: karl.gademann@unibas.ch; Tel: +41 612671144

† Dedicated to Professor Dr Christoph Tamm on the occasion of his 90th birthday.

‡ Electronic supplementary information (ESI) available: For experimental procedures and compound characterization of all new compounds. See DOI: 10.1039/c3cc38783f

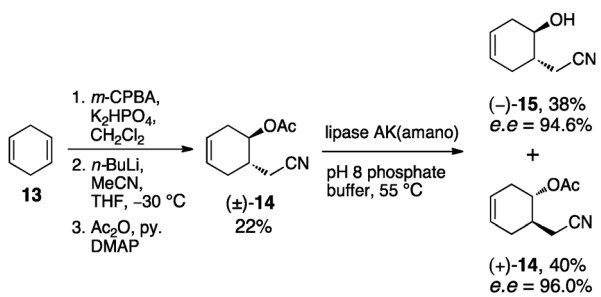


Scheme 1 Retrosynthesis of virosaine A and bubbialidine.

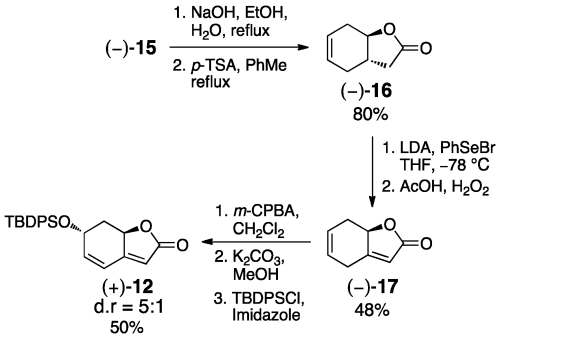
The preparation of silyl-protected aquilegiolide (+)-**12** was carried out following three reported publications (Schemes 2 and 3).[11] The synthesis started with commercially available 1,4-cyclohexadiene **13**. A three step procedure involving mono-epoxidation, ring-opening with cyanomethyllithium and acetylation gave the racemic acetate (±)-**14** in 22% yield. Enzymatic kinetic resolution was then employed to generate enantiomerically enriched alcohol (−)-**15** and acetate (+)-**14** with 94.6% ee and 96.0% ee, respectively.[11a]

Treatment of alcohol (−)-**15** under basic conditions triggered the hydrolysis of the nitrile functionality (Scheme 3). Subsequent acid catalysed lactonisation with *p*-toluenesulfonic acid gave lactone (−)-**16** in 80% yield over two steps. Following phenylselenation and oxidative elimination, butenolide (−)-**17** was accessed in moderate yield.[11b] The silyl protected aquilegiolide (+)-**12** was obtained by diastereoselective epoxidation (dr = 5 : 1), base-induced epoxide opening and silyl protection in good yields over three steps.[11c]

The enantioselective synthesis of virosaine A (**1**) is described in Scheme 4. The first key transformation, a vinylogous Mannich reaction,[12] between (+)-**12** and aminol **11**[13] was achieved using triisopropylsilyl triflate as a Lewis acid, an elegant methodology reported by Busqué and coworkers.[11c] This resulted in the formation of solely two diastereoisomers (among the four possible) in



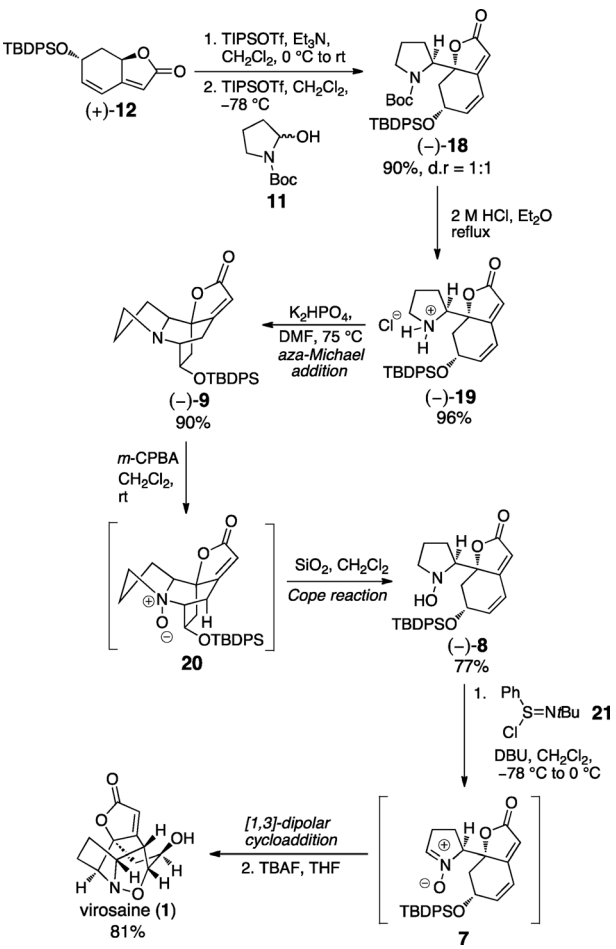
Scheme 2 Enantioselective synthesis of (−)-**15** and (+)-**14**.



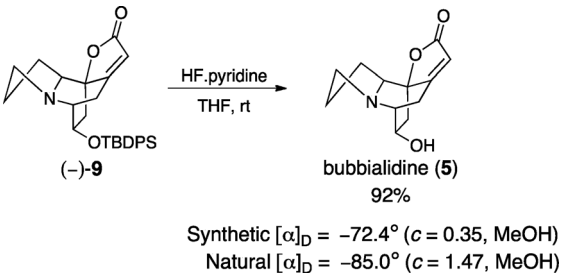
Scheme 3 Synthesis of butenolide **12**.

1 : 1 ratio in a yield of 90%. Pleasingly, the two isomers were separable by column chromatography allowing clean isolation of the desired adduct (−)-**18**. The Boc group was smoothly removed using a hydrogen chloride solution to give (−)-**19** in a quantitative yield. To our surprise, the treatment of HCl salt (−)-**19** with potassium hydrogenphosphate at elevated temperature facilitated an intramolecular aza-Michael addition[14] to furnish the tetracycle (−)-**9** in a remarkable yield of 90%.

This transformation enabled efficient formation of *N*-oxide **20** (supported by ^{1}H-NMR characterization) in the next step using *m*-chloroperbenzoic acid and the alkene functionality was



Scheme 4 Enantioselective synthesis of virosaine A (**1**).



Scheme 5 Enantioselective synthesis of bubbialidine (**5**).

revealed under slightly acidic conditions to yield *N*-hydroxypyrrolidine (−)-**8** in 77% yield over two steps.[15] The next step was the construction of the nitrone unit **7** utilizing a convenient and mild method developed by Mukaiyama and coworkers.[16]

Gratifyingly, the use of *N*-*t*-butylbenzenesulfinimidoyl chloride **21**[17] at −78 °C resulted in a complete regioselective formation of nitrone **7** due to steric encumbrance and an immediate intramolecular [1,3]-dipolar cycloaddition[15a,18,19] was observed. Finally, the removal of silyl group was performed using tetrabutylammonium fluoride to give virosaine A (**1**) in a good yield of 81% over two steps. The synthetic virosaine A (**1**) displayed identical physical and spectroscopic data to those reported in the literature.[2] In addition, the first synthesis of bubbialidine (**5**) was also accomplished by silyl deprotection of tetracycle (−)-**9** to give the target natural product in 92% yield (Scheme 5). The synthetic sample displayed identical physical and spectroscopic data to the reported values.[9]

In summary, we report the first enantioselective total syntheses of virosaine A (**1**) and bubbialidine (**5**). The synthesis of virosaine A was achieved in 18 steps whereas bubbialidine was synthesized in 15 steps starting from readily available material. Our synthetic strategy can be highlighted by the intramolecular aza-Michael addition for the construction of the tetracycle (−)-**9**, Cope-elimination for a late-stage oxidation of the pyrrolidine unit, and an intramolecular cycloaddition reaction to build the 7-oxa-1-azabicyclo[3.2.1]octane ring core. Further application of this approach towards related natural products is currently under investigation.

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