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Enantioselective total synthesis of virosaine A and bubbialidine^{†‡}

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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 birdege-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

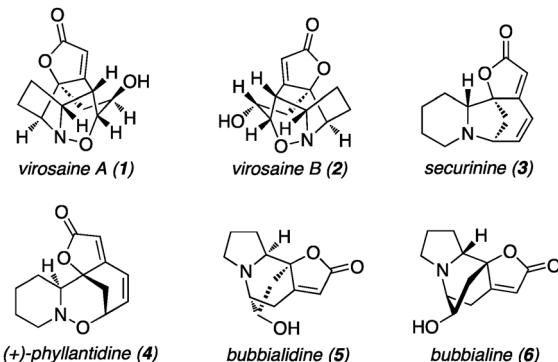


Fig. 1 Virosaines A, B and examples of related alkaloids.

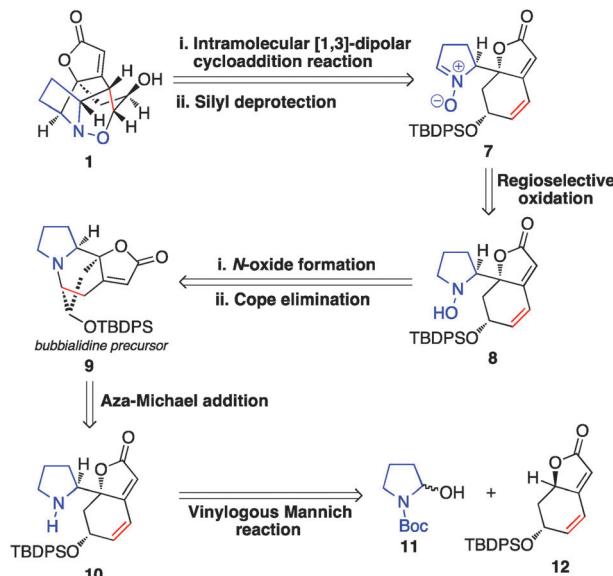
alkaloids bubbialidine (5) and bubbialine (6) were isolated from the leaves of *Zygogynum pauciflorum* by Potier *et al.* in 1990.⁹ There is no reported publication for the synthesis of virosaine A and bubbialidine to date. In this communication, we report the first total syntheses of virosaine A (1) 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.

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† 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

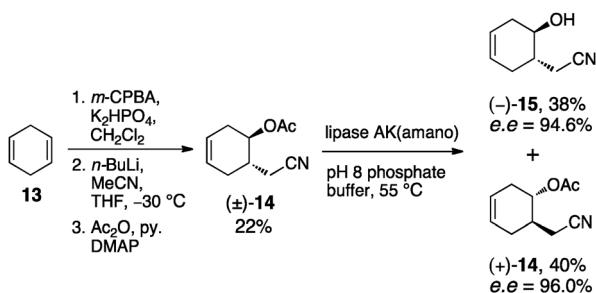
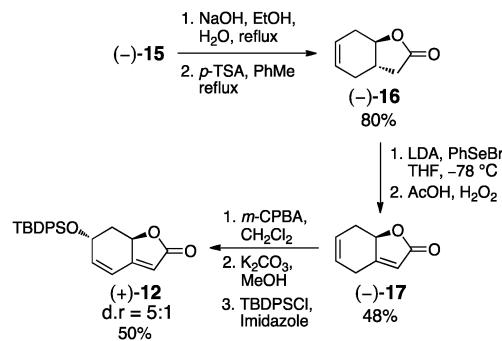


Scheme 1 Retrosynthesis of virosaine A and bubbialidine.

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 cyanomethylolithium and acetylation gave the racemic acetate (\pm) -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 phenyl-selenation and oxidative elimination, butenolide $(-)$ -17 was accessed in moderate yield.^{11b} The silyl protected aquilegiolide $(+)$ -12 was obtained by diastereoselective epoxidation (*d.r.* = 5 : 1), base-induced epoxide opening and silyl protection in good yields over three steps.^{11c}

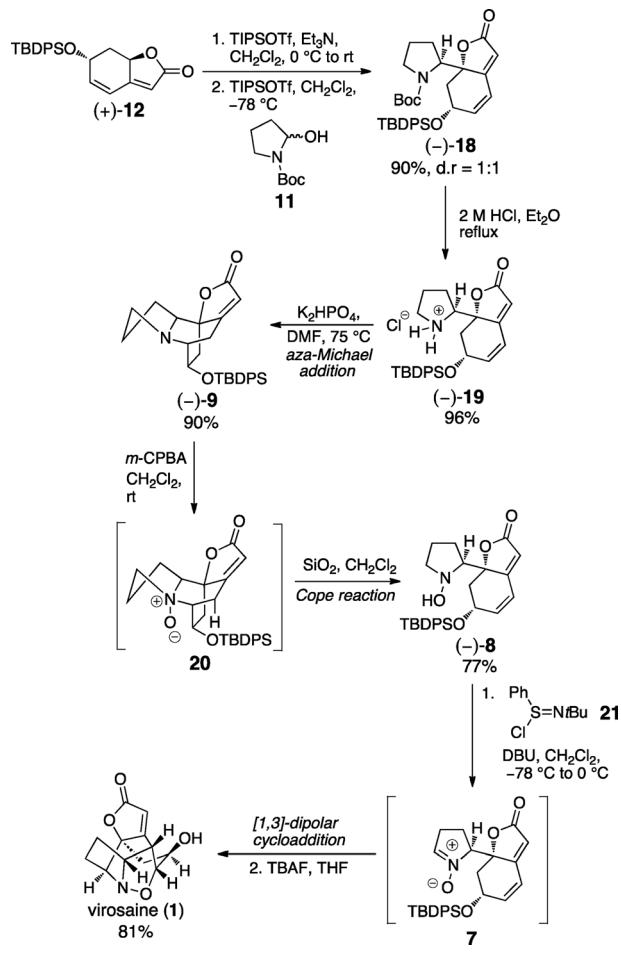
The enantioselective synthesis of virosaine A (1) is described in Scheme 4. The first key transformation, a vinylogous Mannich reaction,¹² between $(+)$ -12 and aminol 11¹³ was achieved using triisopropylsilyl triflate as a Lewis acid, an elegant methodology reported by Busqué and coworkers.^{11c} This resulted in the formation of solely two diastereoisomers (among the four possible) in

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

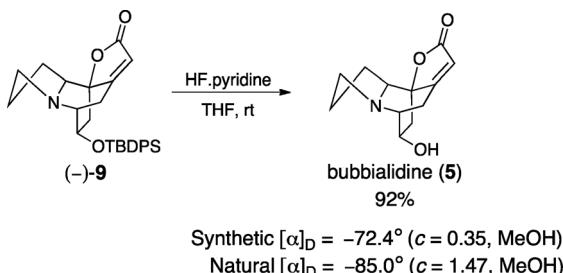
Scheme 3 Synthesis of butenolide 12.

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 addition¹⁴ 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 21¹⁷ 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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