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. 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). 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, 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 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.
The preparation of silyl-protected aquilegiolide (+)-12 was carried out following three reported publications (Schemes 2 and 3).\textsuperscript{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.\textsuperscript{11}

Treatment of alcohol (±)-15 under basic conditions triggered the hydrolysis of the nitrile functionality (Scheme 3). Subsequent acid catalysed lactonisation with p-toluenesulphonic acid gave lactone (±)-16 in 80% yield over two steps. Following phenyl-selenation and oxidative elimination, butenolide (±)-17 was accessed in moderate yield.\textsuperscript{11}\textsuperscript{b} 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.\textsuperscript{11}\textsuperscript{c}

The enantioselective synthesis of virosaine A (1) is described in Scheme 4. The first key transformation, a vinylogous Mannich reaction,\textsuperscript{12} between (+)-12 and aminol 11\textsuperscript{13} was achieved using trisopropylsilyl triflate as a Lewis acid, an elegant methodology reported by Busqué and coworkers.\textsuperscript{11}\textsuperscript{c} This resulted in the formation of solely two diastereoisomers [among the four possible] in a 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\textsuperscript{14} to furnish the tetracycle (−)-9 in a remarkable yield of 90%.

This transformation enabled efficient formation of N-oxide 20 (supported by 1H-NMR characterization) in the next step using m-chloroperbenzoic acid and the alkene functionality was...
revealed under slightly acidic conditions to yield N-hydroxy-
pyrrolidine (−)-8 in 77% yield over two steps.\textsuperscript{15} The next
step was the construction of the nitrone unit utilizing a convenient
and mild method developed by Mukaiyama and coworkers.\textsuperscript{16}

Gratifyingly, the use of N-t-butylbenzenesulfinimidoyl chloride
21\textsuperscript{17} at −78 °C resulted in a complete regioselective formation of
nitrogen 7 due to steric encumbrance and an immediate intramolecu-
al [1,3]-dipolar cycloaddition\textsuperscript{15c,18,19} was observed. Finally,
the removal of silyl group was performed using tetrabutylammo-
nium 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.\textsuperscript{2} In addition,
the next step synthesis of bubbialidine (5) was also accomplished by silyl
deprotection of tetraycl (−)-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.\textsuperscript{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 tetraycl (−)-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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