ChemComm

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

Enantioselective total synthesis of virosaine A and bubbialidine†‡

Cite this: *Chem. Commun.*, 2013, **49**, 1921

Received 7th December 2012, Accepted 17th January 2013

DOI: 10.1039/c3cc38783f

www.rsc.org/chemcomm

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 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**).

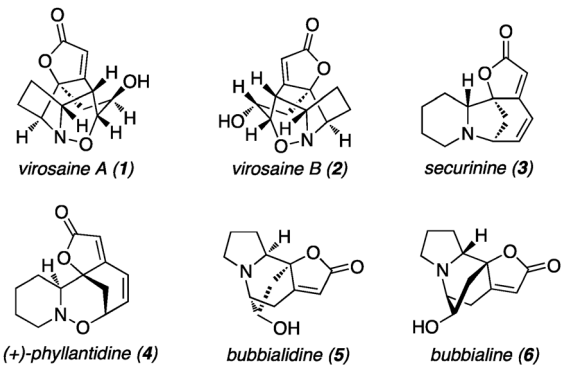


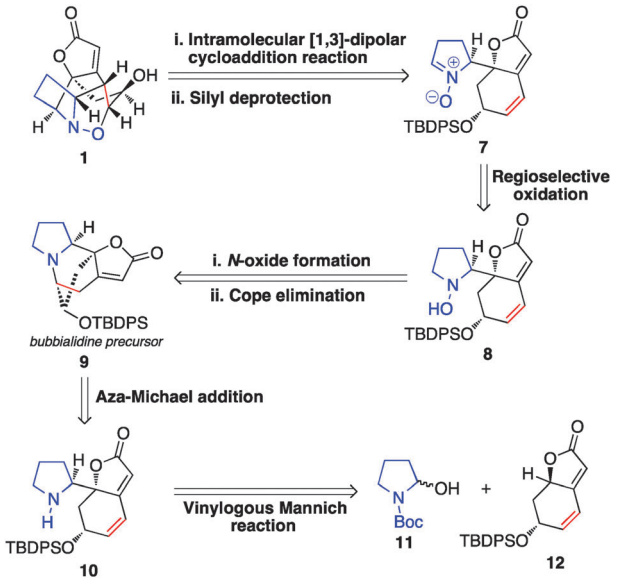
Fig. 1 Virosaines A, B and examples of related alkaloids.

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

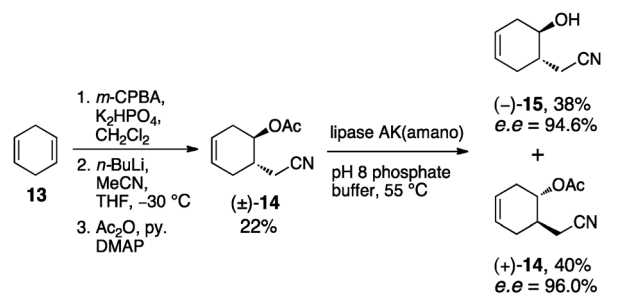


Scheme 1 Retrosynthesis of virosaine A and bubbialidine.

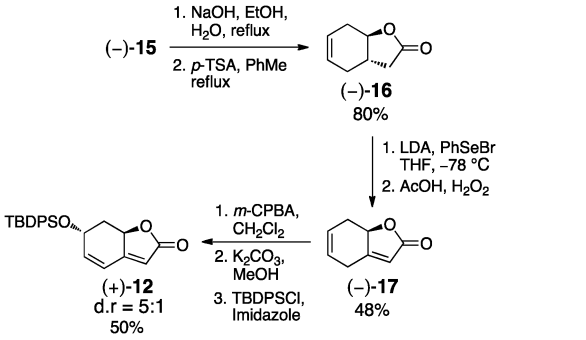
The preparation of silyl-protected aquilegiolide (+)-**12** was carried out following three reported publications (Schemes 2 and 3).[11] The synthesis started with commercially available 1,4-cyclohexadiene **13**. A three step procedure involving mono-epoxidation, ring-opening with cyanomethyllithium 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



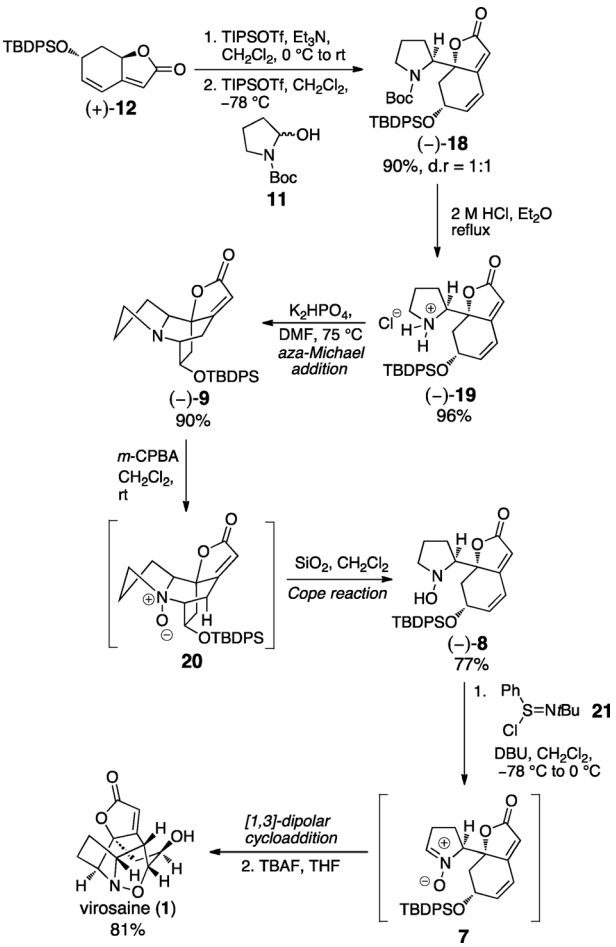
Scheme 2 Enantioselective synthesis of (−)-**15** and (+)-**14**.



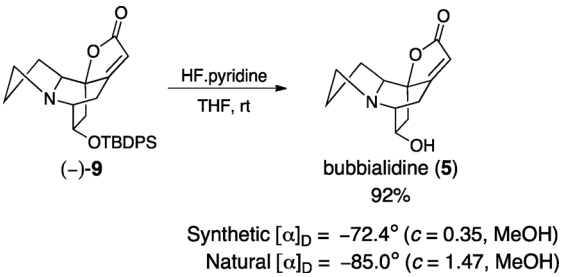
Scheme 3 Synthesis of butenolide **12**.

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*-hydroxy-pyrrolidine (−)-**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.

We thank the Latsis Foundation for support of this work (National Latsis Prize 2011 to K.G.).

Notes and references

1 (*a*) V. Snieckus, in *The Alkaloids*, ed. R. H. F. Manske, Academic Press, New York, 1973, vol. 14, pp. 425–503; (*b*) S. M. Weinreb, *Nat. Prod. Rep.*, 2009, **26**, 758; (*c*) J. A. Beutler and A. N. Brubaker, *Drugs Future*, 1987, **12**, 957–976.
2 B.-X. Zhao, Y. Wang, D.-M. Zhang, X.-J. Huang, L.-L. Bai, Y. Yan, J.-M. Chen, T.-B. Lu, Y.-T. Wang, Q.-W. Zhang and W.-C. Ye, *Org. Lett.*, 2012, **14**, 3096.
3 D. Rognan, T. Boulanger, R. Hoffmann, D. P. Vercauteren, J.-M. Andre, F. Durant and C.-G. Wermuth, *J. Med. Chem.*, 1992, **35**, 1969.
4 (*a*) E. Galvez-Ruano, M. H. Aprison, D. H. Robertson and K. B. Lapkowitz, *J. Neurosci. Res.*, 1995, **42**, 666; (*b*) H. Weenen, M. H. H. Nkunya, D. H. Bray, L. B. Mwasumbi, L. S. Kinabo, V. A. Kilimali and J. B. Wijnberg, *Planta Med.*, 1990, **56**, 371; (*c*) J. L. Mensah, I. Lagarde, C. Ceschin, G. Michel, J. Gleye and I. Fouraste, *J. Ethnopharmacol.*, 1990, **28**, 129; (*d*) H. Tatematsu, M. Mori, T.-H. Yang, J.-J. Chang, T. T.-Y. Lee and K.-H. Lee, *J. Pharm. Sci.*, 1991, **80**, 325.
5 For an early review of the biological activities of these alkaloids, see: J. A. Beutler and A. N. Brubaker, *Drugs Future*, 1987, **12**, 957.
6 (*a*) S. Saito, H. Yoshikawa, Y. Sato, H. Nakai, N. Sugimoto, Z. Horii, M. Hanaoka and Y. Tamura, *Chem. Pharm. Bull.*, 1966, **14**, 313; (*b*) T. Honda, H. Namiki, M. Kudoh, N. Watanabe, H. Nagase and H. Mizutani, *Tetrahedron Lett.*, 2000, **41**, 5927; (*c*) S. Liras, J. E. Davoren and J. Bordner, *Org. Lett.*, 2001, **3**, 703; (*d*) B. Dhudshia, B. F. T. Cooper, C. L. B. Macdonald and A. N. Thadani, *Chem. Commun.*, 2009, 463.
7 C. A. Carson and M. A. Kerr, *Angew. Chem., Int. Ed.*, 2006, **45**, 6560.
8 H. Wei, C. Qiao, G. Liu, Z. Yang and C.-C. Li, *Angew. Chem., Int. Ed.*, 2013, **52**, 620.
9 A. Ahond, J. Guilhem, J. Hamon, J. Hurtado, C. Poupat, J. Pusset, M. Pusset, T. Sévenet and P. Potier, *J. Nat. Prod.*, 1990, **53**, 875. For the isolation of related natural products, see: (*a*) P. J. Houghton, T. Z. Woldemariam, S. O'Shea and S. P. Thyagarajan, *Phytochemistry*, 1996, **43**, 715; (*b*) J. R. Patela, P. Tripathib, V. Sharmaa, N. S. Chauhana and V. K. Dixit, *J. Ethnopharmacol.*, 2011, **138**, 286.
10 P. Magnus, J. Ródriguez-López, K. Mulholland and I. Matthews, *Tetrahedron*, 1993, **49**, 8059.
11 (*a*) N. Kato, M. Inada, H. Sato, S. Ito, M. Shoji and M. Ueda, *Tetrahedron Lett.*, 2007, **48**, 7702; (*b*) G. Audran and K. Mori, *Eur. J. Org. Chem.*, 1998, 57; (*c*) G. G. Bardaji, M. Canto, R. Alibes, P. Bayon, F. Busqué, P. De March, M. Figueredo and J. Font, *J. Org. Chem.*, 2008, **73**, 7657.
12 For applications of vinylogous Mannich reactions to alkaloid synthesis, see: (*a*) S. Martin and A. Liras, *J. Am. Chem. Soc.*, 1993, **115**, 10450; (*b*) S. F. Martin, C. W. Clark and J. W. Corbett, *J. Org. Chem.*, 1995, **60**, 3236; (*c*) S. F. Martin, C. W. Clark, M. Ito and M. Mortimore, *J. Am. Chem. Soc.*, 1996, **118**, 9804; (*d*) S. F. Martin and S. K. Bur, *Tetrahedron*, 1999, **55**, 8905; (*e*) S. F. Martin, K. J. Barr, D. W. Smith and S. K. Bur, *J. Am. Chem. Soc.*, 1999, **121**, 6990. For a review of the Mannich reaction, see: (*f*) M. Arend, B. Westermann and N. Risch, *Angew. Chem., Int. Ed.*, 1998, **37**, 1045; (*g*) S. K. Bur and S. F. Martin, *Tetrahedron*, 2001, **57**, 3221.
13 S. Peixoto, T. M. Nguyen, D. Crich, B. Delpech and C. Marazano, *Org. Lett.*, 2010, **12**, 4760.
14 For recent reviews in this area, see: (*a*) D. Enders, C. Wang and J. X. Liebich, *Chem.–Eur. J.*, 2009, **15**, 11058; (*b*) P. R. Krishna, A. Sreeshailam and R. Srinivas, *Tetrahedron*, 2009, **65**, 9657; (*c*) J. Wang, P. Li, P. Y. Choy, A. S. C. Chan and F. Y. Kwong, *ChemCatChem*, 2012, **4**, 917.
15 For examples of synthesis of *N*-hydroxy-pyrrolidines through Cope elimination, see: (*a*) J. J. Tufariello, *Acc. Chem. Res.*, 1979, **12**, 396; (*b*) I. A. O'Neil, E. Cleator and D. J. Tapolczay, *Tetrahedron Lett.*, 2001, **42**, 8247; (*c*) I. A. O'Neil, E. Cleator, V. E. Ramos, A. P. Chorlton and D. J. Tapolczay, *Tetrahedron Lett.*, 2004, **45**, 3655; (*d*) G. L. Ellis, I. A. O'Neil, V. E. Ramos, S. B. Kalindjian, A. P. Chorlton and D. J. Tapolczay, *Tetrahedron Lett.*, 2007, **48**, 1687.
16 J. Matsuo, T. Shibata, H. Kitagawa and T. Mukaiyama, *ARKIVOC*, 2001, 58, part (x).
17 For other application of this reagent in organic synthesis, see: (*a*) T. Mukaiyama, J. Matsuo and M. Yanagisawa, *Chem. Lett.*, 2000, 1072; (*b*) T. Mukaiyama, A. Kawana, Y. Fukuda and J. Matsuo, *Chem. Lett.*, 2001, 390; (*c*) J. Matsuo, D. Iida, K. Tatani and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 223; (*d*) N. Z. Burns, I. Krylova, R. N. Hannoush and P. S. Baran, *J. Am. Chem. Soc.*, 2009, **131**, 9172.
18 (*a*) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 565; (*b*) R. Huisgen, *J. Org. Chem.*, 1968, **33**, 2291; (*c*) D. St. C. Black, R. F. Crozier and V. C. Davis, *Synthesis*, 1975, 205. For application of intramolecular 1,3-dipolar cycloaddition in organic synthesis, see the excellent reviews by: (*d*) A. Padwa, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 123; (*e*) A. Padwa and A. M. Schoffstall, *Adv. Cycloaddit.*, 1990, **2**, 1; (*f*) V. Naira and T. D. Suja, *Tetrahedron*, 2007, **63**, 12247.
19 For the preparation of functionalized isoxazolidines using Cope elimination–intramolecular nitrone cycloaddition, see: I. A. O'Neil, V. E. Ramos, G. L. Ellis, E. Cleator, A. P. Chorlton, D. J. Tapolczay and S. B. Kalindjian, *Tetrahedron Lett.*, 2004, **45**, 3659.