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A Concise, Enantioselective Total Synthesis of (–)-Virosaine A

*Jonathan M. E. Hughes and James L. Gleason**

Abstract: *The total synthesis of (–)-virosaine A (**1**) was achieved in 10 steps starting from furan and 2-bromoacrolein. A one-pot Diels-Alder cycloaddition/organolithium addition initiated an efficient sequence to access a key oxime/epoxide intermediate. Heating this intermediate in acetic acid resulted in an intramolecular epoxide opening/nitrone [3+2] cycloaddition cascade to construct the caged core of **1** in a single step. Several methods of C-H functionalization were assessed on the cascade product and, ultimately, a directed lithiation/bromination effected selective C14 functionalization to enable the synthesis of **1**.*

The *Securinega* alkaloids are a broad class of natural products that are distributed among plants of the Euphorbiaceae family and, owing to their fascinating structural features and biological activities, have been the target of many successful and elegant total synthesis efforts.[1] Recently, some of the most structurally complex *Securinega* alkaloids were isolated from *Flueggea virosa*, a large shrub widely distributed in southern China and known for its use in the treatment of eczema, allergic dermatitis and scald.[2] Among these new alkaloids, virosaine A (**1**) and B (**2**) were noted for containing the most highly caged structures of the *Securinega* class (Figure 1A).[3] The proposed biosynthesis of the polycyclic virosaine core is particularly noteworthy, as it is believed to involve a [3+2] nitrone cycloaddition, a transformation that is rare in alkaloid biosynthesis.[4,5,6,7,8] The caged pentacyclic frameworks of **1** and **2** have made them attractive yet challenging targets for total synthesis. To date, there has been only one reported synthesis of **1** and **2**, in 18 and 10 steps respectively.[5a,5b] In both cases, the strategies relied on *N*-oxidation of another *Securinega* alkaloid (*O*-silylated bubbialidine and allonorsecurinine, respectively) to furnish a nitrone that engaged in the putative biosynthetic [3+2] cycloaddition as the final step. Here, we describe a highly concise approach to **1** that exploits a selective late-stage modification of an unactivated C(sp^3)-H bond of a polycyclic core that is rapidly assembled via a cascade epoxide opening/nitrone cycloaddition.

In examining **1**, we envisaged that the alcohol and enoate functional groups might be mutually masked via an ether bridge, leading to caged hexacycle **3** (Figure 1B). Further, cleavage of the C13-C14 bond (*vide infra*) results in key intermediate **4**, the caged core of **3**, which might arise by a bio-inspired [3+2] cycloaddition of nitrone **5**. We envisioned that **5** could be generated in a stereo- and regiocontrolled fashion by opening of an epoxide with a pendant oxime, a process that might be incorporated in tandem with the nitrone cycloaddition (**6→5→4**). Finally, cascade precursor **6** might be produced efficiently beginning with Corey's asymmetric Diels-Alder cycloaddition of 2-bromoacrolein (**9**) with furan (**8**).[9] Importantly, cycloaddition of **9** is limited to furan itself, with substituted furans leading only to Michael addition products, making early stage introduction of functionality necessary for the butanolide in **3** impossible. Thus, the success of the nitrone formation/cycloaddition cascade strategy ultimately hinged on the ability to selectively functionalize **4** at C14. Late-stage C-H functionalization is an increasingly powerful tool for the synthesis of complex natural products and recent progress in the areas of carbene and nitrene insertio and C-H oxidation chemistry, in particular, have provided powerful ne additions to the arsenal of potential strateg transformations.[10,11,12,13,14,15] While their application in comple molecule settings is often challenging, it can enable more efficie overall strategies. In the present context, while late stage regio- an chemoselective manipulation of the unactivated C14-H14 bond in might be difficult due to the presence of 11 other C-H bonds and th basic isoxazolidine, it would enable the epoxide opening/nitron cycloaddition cascade as a viable, concise route to the natural product.

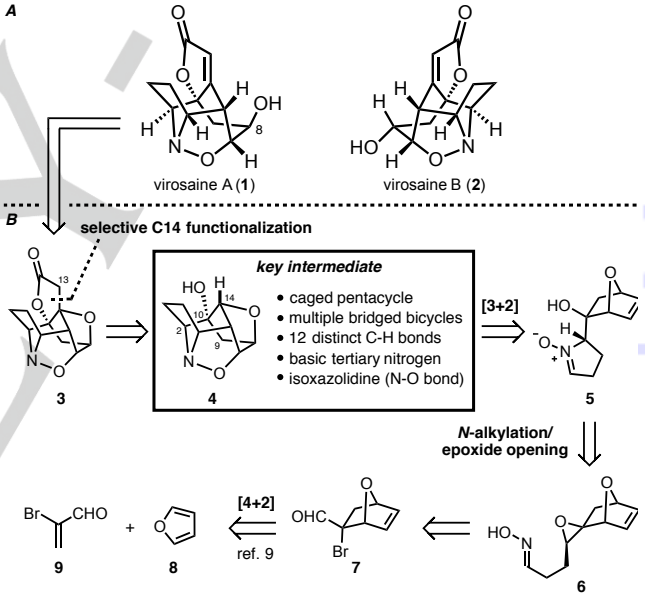

Figure 1. (a) Virosaine A (**1**) and B (**2**) and (b) retrosynthetic analysis of **1**.

Oxabicycle **7** was readily generated by oxazaborolidinone-catalyze cycloaddition of 2-bromoacrolein (**9**) with furan (**8**).[9,16] In our hand and those of others,[16] **7** proved insufficiently stable to isolate. Howeve we found that **7** could be trapped *in situ* by a variety of organolithiu and Grignard reagents to give stable bromohydrin products. In particula addition of organolithium **11** afforded **12** in 62% yield, 2.7:1 d.r. an 83% *ee*.[17] Screening of alternative conditions (nucleophile, additive, solvent, etc.) did not improve diastereoselectivity further. Although the diasteromers of **12** could not be separated chromatographically, recrystallization gratifyingly provided alcohol **12** in >20:1 d.r. and >99% *ee*.[18] This one-pot process served to install all but two carbons of the final natural product. Subsequent acid-promoted dioxolane cleavage to give lactol **13** was followed by condensation with $TBSONH_2$ to provide *O*-silyl oxime **14** in 92% yield over two steps. Epoxide formation then proceeded smoothly upon treatment with NaH to afford **15** in near quantitative yield.

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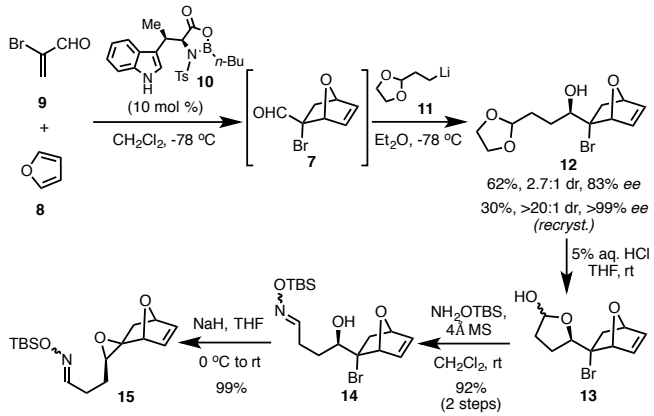
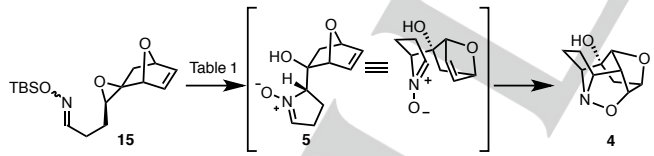


Scheme 1. Enantioselective synthesis of cascade precursor **15**.

With epoxide **15** in hand, we turned our attention to the key epoxide opening/nitrone cycloaddition cascade reaction sequence (Table 1). There is limited literature precedent for this type of cascade and, to the best of our knowledge, application to access a bridged polycyclic ring system is unprecedented.[19] Initially, we observed that oxime addition to the epoxide in **15** required prolonged heating at high temperatures under neutral conditions. Advantageously, the use of mild protic acids, such as pyridinium *p*-toluenesulfonate (PPTS), promoted rapid epoxide opening to form nitrone **5**. Furthermore, when the reaction was conducted in xylenes at 140 °C, nitrone **5** underwent the desired [3+2] cycloaddition directly to give **4** in 26% overall yield (entry 1). Encouraged by these results, we screened a variety of solvents for the transformation and found that THF and MeCN improved the yield significantly in combination with microwave heating (entries 3 and 5). Gratifyingly, further screening revealed that, while acetic acid was not an efficient promoter when employed in acetonitrile (entry 6), the reaction conducted in acetic acid as solvent afforded **4** in a remarkable 92% yield in one pot from **15** (entry 7). Overall, this novel cascade process allowed us to access the complex core of virosaine A (**1**) in only 5 steps from commercially available materials.

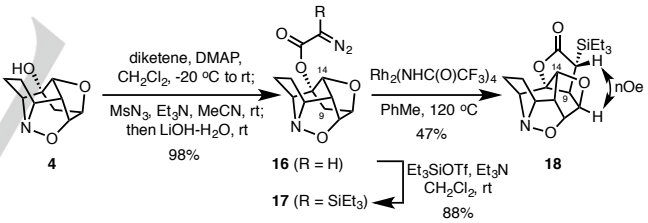
Table 1. Cascade reaction sequence optimization.



Entry	Solvent	Acid (equiv.)	T (°C)	Time	Yield (%)[a]
1[b]	xylenes	PPTS (0.2)	140	8 h	26
2	THF	PPTS (1)	70	12 h	40
3[c]	THF	PPTS (1)	100	1 h	45
4[c]	MeOH	PPTS (1)	120	1 h	28
5[c]	MeCN	PPTS (1)	120	1 h	50
6[c]	MeCN	AcOH (5)	120	1 h	<10
7[c]	**AcOH**	**-**	**120**	**30 min**	**92**
8[d]	AcOH	-	120	40 min	82

[a] Isolated yields of **4**. [b] Oxime **6** used as starting material. [c] Microwave heating. [d] 5 mmol scale.

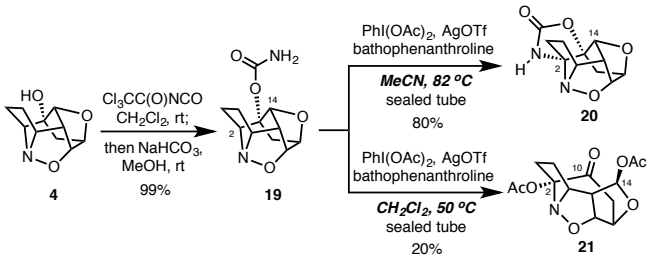
With an efficient route to the virosaine core in hand, the final obstacle was to selectively functionalize C14 of bridged pentacycle **4** to install the butanolide ring. Owing to the significant challenges of regio- and chemoselectivity, we opted to use the C10 hydroxyl as a tether for intramolecular functionalization to limit the potential sites of reactivity to C2, C9 and (the desired) C14 (see **4**, Figure 1B). The most attractive possibility for tethered functionalization was an intramolecular carbene C-H insertion of an α-diazoacetate to directly deliver **3**. Given that there are very few reports of related carbene insertions into bridgehead positions, we were cognizant of the potential difficulties associated with this strategy.[11e,20] Nonetheless, we felt that such a direct approach to access virosaine A warranted investigation. Accordingly, diazoacetate **16** was prepared from **4** in one pot via sequential diketene addition, diazo transfer, and deacetylation (Scheme 2). However, under a range of carbene generating conditions (Rh^{2+}, Cu^{2+}, hν), we observed only formation of complex mixtures from which no clean products could be isolated. Since α-silyl diazoacetates have been shown to attenuate C-H insertion reactivity, we prepared triethylsilyl diazoacetate **17** by silylation of **16**.[20c] Carbene insertion reactions of **17** were cleaner than those of the parent **16** and we were able to effect a C-H insertion using a variety of metal catalysts, with $Rh_2(NHC(O)CF_3)_4$ providing the product in the highest isolated yield. Unfortunately, structural analysis revealed that the carbene insertion had occurred at the C9 methylene instead of the desired C14 methine, affording α-silyllactone **18**.



Scheme 2. Carbene C-H insertion reaction of diazoacetate **17**.

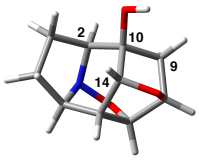
Given the undesirable site-selectivity of the carbene insertion, w explored the potential of a nitrene C-H insertion to functionalize C1 Although this would not install the lactone directly, the resulting amin might be hydrolyzed to a ketone suitable for subsequent manipulatio Furthermore, we were encouraged by several reports of nitren insertions into bridgehead C-H bonds in complex molecu settings.[11a,11f,21] To this end, carbamate **19** was prepared by treatin alcohol **4** with $Cl_3CC(O)NCO$ followed by $NaHCO_3$/MeOH (Scheme 3 With **19** in hand, we surveyed several sets of conditions and found th He's conditions ($PhI(OAc)_2$, AgOTf, bathophenanthroline, MeCN, 8 °C) provided a single product, which was identified as oxazolidinone **20**.[11f,21,22] In contrast to the selectivity observed in the carbene insertion, oxidative functionalization of carbamate **19** occurred at C2, a result that highlights the sensitivity of the system to the nature of the reactive intermediate (carbenoid vs. nitrenoid). All attempts to deactivate C2 by protonation or BF_3 coordination of the isoxazolidine nitrogen did not alter the selectivity of the insertion process.[23] Interestingly, we found that the same reaction, conducted in CH_2Cl_2 instead of MeCN,

exclusively generated ketone **21**, whose formation is the result of both C2 oxidation and C10-C14 bond cleavage.



Scheme 3. Oxidative transformations of carbamate **19**.

The lack of reactivity at C14 in both the carbene and nitrene chemistry is likely due to a combination of unfavourable sterics and stereoelectronics. In particular, the inability of the lone pair from the bridging oxygen to donate into the C14-H14 σ* orbital presumably results in only inductive deactivation by the electronegative oxygen.[11e] Indeed, assessing the three potential sites of reactivity by both DFT and NMR chemical shift analysis, methods which have been used previously to predict site-selectivity for radical and oxidative functionalizations,[11c,11g,24,25] provide support for low reactivity of C14. NMR analysis revealed that both H14 and C14 are the most downfield signals in **4**, suggesting that the position is electron poor. Also consistent with this notion, NPA charge analysis indicated that C14 has a relatively high positive charge and NBO analysis indicated that the C14-H14 bond has the lowest energy HOMO of all the C-H bonds in **4**.[26]

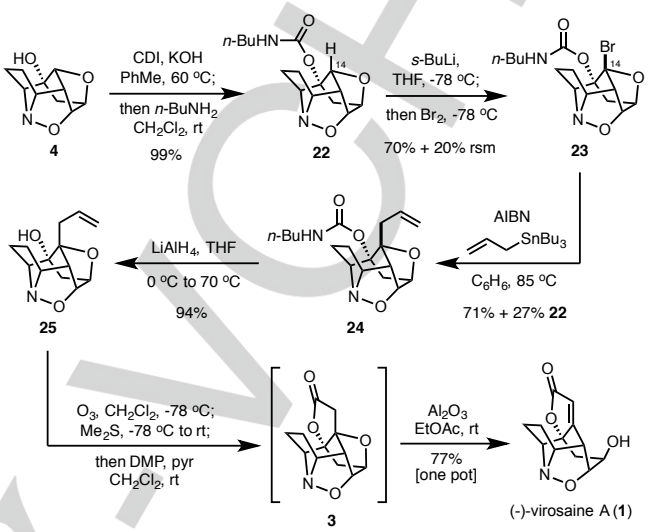


4: "top-down" perspective

Site	^{1}H (δ, ppm)	^{13}C (δ, ppm)	NPA partial atomic charge on carbon	C-H HOMO Energy (eV)
2	3.59	66.8	-0.037	-13.69
9	1.73	45.5	-0.423	-13.71
14	4.72	85.7	+0.095	-14.48

Figure 2. Evaluation of the potential sites of reactivity in **4** using NMR chemical shift assessment and natural population analysis (NPA)/natural bond orbital (NBO) analysis of the energy minimized structure determined at B3LYP/6-311++G** theory level.

Given the electron deficient nature of C14, we reasoned that it might be possible to carry out a site-directed deprotonation to functionalize this position.[27] Indeed, we were delighted to find that carbamate **22**, prepared via sequential treatment of **4** with carbonyl diimidazole and *n*-$BuNH_2$, could be lithiated selectively at C14 using 2.2 equivalents of *s*-BuLi (Scheme 4). Subsequent quenching of this lithiated species with Br_2 led exclusively to alkyl bromide **23** in good yield.[28] With a functional handle at C14 in place, butanolide ring construction and the completion of the total synthesis was within reach. Radical allylation employing Keck's conditions smoothly delivered allylated carbamate **24** in 71% yield.[29] The remaining mass balance of the reaction was reduction product **22**, which was conveniently recycled. Removal of the carbamate using $LiAlH_4$ then provided alcohol **25** in excellent yield without any concurrent N-O bond cleavage, setting the stage for the final annulation event. Ozonolysis of **25** produced a lactol, which was immediately oxidized to lactone **3**. Exposure of **3** to activated neutral Al_2O_3 delivered (-)-virosaine A (**1**) in 77% yield (one pot) from **25**.



Scheme 4. Synthesis of (-)-virosaine A (1).

In conclusion, we have achieved the shortest enantioselective tot synthesis of (-)-virosaine A (**1**) in 9% overall yield. The route features a efficient epoxide opening/nitrone cycloaddition cascade reactic sequence to rapidly construct the core of **1**. The successfi implementation of this strategy hinged on the ability to selectivel manipulate the C14-H14 bond. Several methods of C- functionalization were investigated and highlighted the significant effe that method choice has on regioselectivity in a complex molecu setting. Selective functionalization was ultimately achieved via directed lithiation/bromination sequence, which enabled the completic of the total synthesis in an efficient manner.

Acknowledgements

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Keywords: virosaine A • total synthesis • alkaloids • directed lithiation • domino reactions

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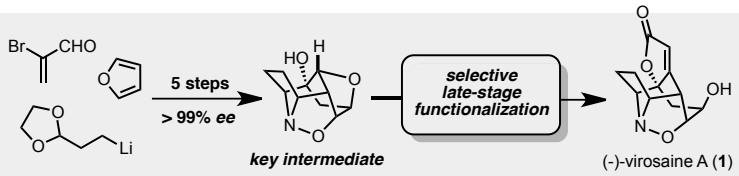

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A Concise, Enantioselective Total Synthesis of (–)-Virosaine A

The core of virosaine A is prepared in 5 short steps via a cycloaddition/organolithium addition and a nitrone formation/cycloaddition cascade. Late-stage selective functionalization of an unactivated C-H via directed lithiation enables conversion of the key intermediate to the natural product.