Asymmetric Total Synthesis of (+)-Virosine A via Sequential Nucleophilic Cyclizations onto an Activated Formamide

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Supporting Information

ABSTRACT: The first synthesis of tetracyclic alkaloid virosine A is reported. The natural alkaloid was prepared in only 13 steps, in an enantioenriched form. The azabicyclo[2.2.2]octane core was efficiently assembled using a key Vilsmeier–Haack and Mannich cyclizations sequence performed in one pot.

INTRODUCTION

Virosine A is a tetracyclic alkaloid from the Securinega family. These alkaloids are isolated from several species of the Euphorbiaceae plant family and are known to act on the central nervous system as γ-aminobutyric acid (GABA) receptor antagonists. Visorine A (1) was isolated by Ye and co-workers in 2008.3 The structure elucidation is essentially based on 1D and 2D NMR data (Figure 1).

Intriguingly, the structure of visorine A is exactly the same as was proposed for securinol B by Arbain and Sargent in 1991.4 In fact, securinol B and its epimer, securinol A, were both initially isolated from Securinega suffriticosa by Tamura and Iwamoto in 1965.5 While securinol A was fully characterized, data about securinol B only allowed the authors to suggest that securinol B was a stereoisomer of securinol A. Based on analogies with more abundant members of this family such as viroallosecurinine (3), an azabicyclo[2.2.2]octane core was initially proposed by the authors (see structures 4 and 5 for securinol B and A, respectively). In 1991, Arbain and Sargent revised the structure of securinol A (2) to an azabicyclo[2.2.2]-octane core skeleton based on X-ray analysis of its hydrobromide salt. Because it was known that both securinol A and B lead to viroallosecurinine (3) upon treatment of their respective mesylate with collidine,6 presumably through the same aziridinium ion 6,4 Arbain and Sargent therefore proposed the revised structure 1 for securinol B even though they had not isolated the latter. When Ye and co-workers reported the isolation of a new alkaloid in the same family in 2008, even though the structure 1 they elucidated matched the one proposed for securinol B, in the absence of sufficient characterization data on securinol B they legitimately proposed another name, virosine A.3 No synthesis of this interesting and rather unusual polycyclic alkaloid is reported to date.

RESULTS AND DISCUSSION

We planned to make use of a cascade of Vilsmeier–Haack and Mannich cyclizations as the key step to assemble the azabicyclo[2.2.2]octane core of the natural product.7 Scheme 1 shows our retrosynthetic analysis of virosine A (1). The latter could be derived from intermediate 7, which in turn could be obtained upon chemoselective amide activation of formamide 8, generating two rings and two of the four stereocenters of virosine A. Intermediate 8 would be obtained after functional group manipulation on amine 9 and enolization of the butenolide ring. The latter would be the product of an intramolecular olefination. Finally, azido-alcohol 10 would be prepared by desymmetrization of meso-epoxide 11 and functionalization of the alkene moiety.

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We already have disclosed our approach to the core of virosine A (securinol B) (Scheme 2). In this first generation approach, we demonstrated the viability of the key Vilsmeier−Haack/Mannich cyclizations to generate a tricyclic product 15 in a racemic form. Only 11 steps were required to access this advanced intermediate. Unfortunately, all attempts to install the butenolide ring of virosine A from 15 failed.

From these initial results, it became clear that a butenolide precursor needed to be installed prior to the key biscyclization. Hence, the furyl group was elected because it offers both the possibility to generate directly the butenolide in the key step and a suitable nucleophilicity. In a second generation approach (Scheme 3), the furyl was installed from intermediate 13.

Hence, we developed a third generation approach, which turned out to be much more efficient and reliable. To access virosine A in a non-racemic form, the synthesis started with the desymmetrization of epoxide 11 using Jacobsen’s conditions to afford enantioenriched azido-alcohol 22 in a 94:6 enantiomeric ratio (Scheme 4), which compares to literature. Compound 22 was submitted to a hydroxy-directed epoxidation followed by protection of the resulting alcohol as a silyl ether. Instead of opening epoxide 12 with bromoacetic acid followed by an Arbuzov reaction (as we did in the second generation approach, Scheme 3), the epoxide 12 was rather opened with diethyl phosphonoacetic acid, and the desired phosphonoester 10 was

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generated in one step (Scheme 4). Again, only one diastereomer and regioisomer for the opening of epoxide 12 was observed, for the reason explained in Scheme 5: the opening through Route a leads to a twist-boat-like transition state, higher in energy than the chair-like transition state for the opening following Route b (preferred). Oxidation of the resulting alcohol 10 using Dess−Martin periodinane furnished the corresponding ketone 24 in high yield (Scheme 4). Then, intramolecular Horner−Wadsworth−Emmons olefination promoted by t-BuOK gave butenolide 25 in 60% yield, along with 11% of product 26 that suffered N3 elimination from 25. The azide was reduced via a catalytic hydrogenation, and the resulting amine 9 was initially formylated. However, all attempts to alkylate the resulting formamide failed, presumably due to steric hindrance engendered by the adjacent OTIPS. Taking advantage of this steric encumbrance, substrate 9 was cleanly monoalkylated (no dialkylation observed) and then formylated. Enolization of butenolide 21 generated the key step precursor 8, now in 10 steps from 11 instead of 14 steps as in the second generation approach.

Upon activation of formamide 8 with triflic anhydride (1.5 equiv) in the presence of 2,6-di-tert-butyl-4-methylpyridine (3 equiv) as the base, the Vilsmeier−Haack cyclization of the furyl proceeded smoothly at rt over 20 min, and the addition of a bromide salt (10 equiv) triggered a Mannich cyclization of the alkyne. The optimized14 one-pot Vilsmeier−Haack and Mannich cyclizations generated amine 7 containing the tetracyclic core of the natural product in 58% yield, in a separable 5:1 mixture with epimeric adduct 27. The stereochemical assignment of compound 7 was done by NOESY experiments that showed correlations for protons indicated in Figure 2. Treatment of vinylic bromide 7 with Pd/C and hydrogen resulted in a fast hydrogenolysis of the C−Br bond, followed by reduction of the resulting disubstituted alkene (Scheme 4). No hydrogenation of the butenolide trisubstituted alkene was observed. It should be noted that the latter alkene is quite hindered on both faces, by the OTIPS (top face) and the piperidine ring (bottom face). Deprotection of the OTIPS ether finally afforded virosine A. The characterization of the synthetic material matched that for the isolated natural product.
**CONCLUSION**

In summary, we demonstrated the use of one-pot Vilsmeier–Haack and Mannich cyclizations as an efficient synthetic strategy for the construction of complex polycyclic alkaloids. This strategy was applied to the first total synthesis of virosine A, prepared in an enantioenriched form in only 13 steps and 3.4% overall yield. We therefore corroborate the absolute configuration deduced by Ye for virosine A. Even though the revised structure proposed by Arban and Sargent for securnolin B is exactly the same as for virosine A, the absence of spectral data for the former does not allow us to conclude that they are indeed the same natural product.

**EXPERIMENTAL SECTION**

**General Information.** All reactions requiring anhydrous conditions were conducted in flame-dried glassware under a dry nitrogen or argon atmosphere. THF was distilled from Na and benzophenone under nitrogen immediately prior to use. Acetonitrile, dichloromethane, benzene, toluene, disopropylethylamine, and triethylamine were distilled from CaH₂ under nitrogen immediately prior to use. Methanol was distilled over 4 Å molecular sieves. Triflic anhydride and tetrabutylammonium fluoride (1.0 M) in DCM were distilled over a small amount of phosphorus pentoxide (P₂O₅) under nitrogen immediately prior to use. THF was distilled from Na and benzophenone under nitrogen immediately prior to use. Azidotrimethylsilane was purified by flash chromatography (silica gel saturated with Et₂O in hexanes) to give 7 (48%) and 10 (9%).

**Experimental.** 3,10-Dien-12-one (7) and (+)-(1559,1563,1567)-7-Aza-4-bromo-13-oxa-15-(trisopropylsilyloxy)tetracyclo[6.5.2.0.012]3,10-dien-12-one (27). Triflic anhydride (15 mg, 0.087 mmol) was added to a solution of formamide 8 (30 mg, 0.058 mmol) and 2,6-di-tert-butyl-4-methylpyridine[16] (36 mg, 0.17 mmol) in CDCl₃ (5.8 mL) at 0 °C. The reaction mixture was stirred at rt for 20 min. Tetrabutylphosphonium bromide (197 mg, 0.577 mmol) and MeCN (5.8 mL) were added, and the mixture was stirred at 70 °C for 15 h. Saturated aq Na₂CO₃ was added, and then the layers were separated. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel saturated with Et₂O in hexanes) to give 7 (13 mg, 48%) and 27 (2.8 mg, 10%).

**For 20 min. Aqueous NaOH (1 N) and EtOAc were added, and layers were separated. The aqueous layer was extracted with the indicated solvent and washed with the indicated aqueous solution, layers were separated. The aqueous phase was then extracted with the indicated solvent. The crude material was purified by flash chromatography (silica gel saturated with Et₂O in hexanes) to give 7 (13 mg, 48%) and 27 (2.8 mg, 10%).

**Summary.** We demonstrated the use of one-pot Vilsmeier–Haack and Mannich cyclizations as an efficient synthetic strategy for the construction of complex polycyclic alkaloids. This strategy was applied to the first total synthesis of virosine A, prepared in an enantioenriched form in only 13 steps and 3.4% overall yield. We therefore corroborate the absolute configuration deduced by Ye for virosine A. Even though the revised structure proposed by Arban and Sargent for securnolin B is exactly the same as for virosine A, the absence of spectral data for the former does not allow us to conclude that they are indeed the same natural product.
under reduced pressure, and the usual purification (10% MeOH in EtOAc) gave 9 (573 mg, 82%) as a white solid: mp 61–64 °C; \( \delta_{1H}^{1H} = 3.76, 2.95, 2.56, 2.52, 2.46, 2.34, 2.17, 1.30, 1.06, 0.92, 0.36, 0.33, 0.31 \text{ ppm} \); HRMS (EI) calcd for \( C_{18}H_{35}N_{3}O_{7}S_{2} \) [M+Na]^{+} 464.1965, 464.1982, 464.1993, 464.1995.

A solution of 6-(triisopropylsilyloxy)cyclohex-3-enylamine (17). To a solution of 6-(triisopropylsilyloxy)cyclohex-3-enylamine (17), \( \delta_{1H}^{1H} = 7.93, 5.38, 5.21, 4.86, 4.64, 4.15, 3.92, 3.80, 3.67, 3.18, 2.80, 2.51, 2.13, 1.92, 1.72, 1.27, 1.06, 0.94, 0.84, 0.33, 0.31 \text{ ppm} \); HRMS (EI) calcd for \( C_{31}H_{57}N_{3}O_{7}S_{2} \) [M+Na]^{+} 480.2978.

rac-(15S,25S,5S)-4-(But-3-ynyl)-5-(triisopropylsilyloxy)-2-oxocyclohexyl bromoacetate (18). To a solution of rac-(15S,25S,5S)-4-(But-3-ynyl)-5-(triisopropylsilyloxy)-2-oxocyclohexyl bromoacetate (18), \( \delta_{1H}^{1H} = 7.91, 7.69, 7.52, 7.28, 7.08, 6.96, 6.74, 6.51, 6.39, 6.26, 6.15, 5.97, 5.51, 5.40, 5.17, 5.02, 4.81, 4.74, 4.64, 4.52, 4.34, 4.05, 3.91, 3.80, 3.66, 3.61, 3.44, 3.33, 3.17, 3.08, 3.02, 2.98, 2.93, 2.88, 2.83, 2.71, 2.67, 2.62, 2.48, 2.41, 2.37, 2.25, 2.19, 2.15, 2.09, 2.02, 1.85, 1.80, 1.76, 1.69, 1.66, 1.62, 1.57, 1.54, 1.50, 1.47, 1.43, 1.40, 1.37, 1.34, 1.31, 1.28, 1.25, 1.21, 1.17, 1.14, 1.10, 1.06, 0.98, 0.94, 0.36, 0.34, 0.32, 0.30, 0.28, 0.26, 0.24, 0.22, 0.20, 0.18, 0.16, 0.14, 0.12, 0.10, 0.08, 0.06, 0.04, 0.02 \text{ ppm} \); HRMS (EI) calcd for \( C_{31}H_{57}N_{3}O_{7}S_{2} \) [M+Na]^{+} 480.2978.

rac-(15S,25S,5S)-4-(But-3-ynyl)-5-(triisopropylsilyloxy)-2-oxocyclohexyl bromoacetate (18). To a solution of rac-(15S,25S,5S)-4-(But-3-ynyl)-5-(triisopropylsilyloxy)-2-oxocyclohexyl bromoacetate (18), \( \delta_{1H}^{1H} = 7.91, 7.69, 7.52, 7.28, 7.08, 6.96, 6.74, 6.51, 6.39, 6.26, 6.15, 5.97, 5.51, 5.40, 5.17, 5.02, 4.81, 4.74, 4.64, 4.52, 4.34, 4.05, 3.91, 3.80, 3.66, 3.61, 3.44, 3.33, 3.17, 3.08, 3.02, 2.98, 2.93, 2.88, 2.83, 2.71, 2.67, 2.62, 2.48, 2.41, 2.37, 2.25, 2.19, 2.15, 2.09, 2.02, 1.85, 1.80, 1.76, 1.69, 1.66, 1.62, 1.57, 1.54, 1.50, 1.47, 1.43, 1.40, 1.37, 1.34, 1.31, 1.28, 1.25, 1.21, 1.17, 1.14, 1.10, 1.06, 0.98, 0.94, 0.36, 0.34, 0.32, 0.30, 0.28, 0.26, 0.24, 0.22, 0.20, 0.18, 0.16, 0.14, 0.12, 0.10, 0.08, 0.06, 0.04, 0.02 \text{ ppm} \); HRMS (EI) calcd for \( C_{31}H_{57}N_{3}O_{7}S_{2} \) [M+Na]^{+} 480.2978.

rac-(15S,25S,5S)-4-(But-3-ynyl)-5-(triisopropylsilyloxy)-2-oxocyclohexyl bromoacetate (18). To a solution of rac-(15S,25S,5S)-4-(But-3-ynyl)-5-(triisopropylsilyloxy)-2-oxocyclohexyl bromoacetate (18), \( \delta_{1H}^{1H} = 7.91, 7.69, 7.52, 7.28, 7.08, 6.96, 6.74, 6.51, 6.39, 6.26, 6.15, 5.97, 5.51, 5.40, 5.17, 5.02, 4.81, 4.74, 4.64, 4.52, 4.34, 4.05, 3.91, 3.80, 3.66, 3.61, 3.44, 3.33, 3.17, 3.08, 3.02, 2.98, 2.93, 2.88, 2.83, 2.71, 2.67, 2.62, 2.48, 2.41, 2.37, 2.25, 2.19, 2.15, 2.09, 2.02, 1.85, 1.80, 1.76, 1.69, 1.66, 1.62, 1.57, 1.54, 1.50, 1.47, 1.43, 1.40, 1.37, 1.34, 1.31, 1.28, 1.25, 1.21, 1.17, 1.14, 1.10, 1.06, 0.98, 0.94, 0.36, 0.34, 0.32, 0.30, 0.28, 0.26, 0.24, 0.22, 0.20, 0.18, 0.16, 0.14, 0.12, 0.10, 0.08, 0.06, 0.04, 0.02 \text{ ppm} \); HRMS (EI) calcd for \( C_{31}H_{57}N_{3}O_{7}S_{2} \) [M+Na]^{+} 480.2978.
MeCN (9 mL) was added to a solution of amine (1H), 4.60 (m, 2.1H); 13C NMR (100 MHz, CDCl3) δ 30.1 (td, J = 22.3, 11.2, 6.6 Hz, 2H), 25.8 (td, J = 22.3, 11.2, 6.6 Hz, 2H), 24.9 (s, 2H), 21.5 (s, 2H), 16.0 (s, 1H), 12.6 (s, 1H). 1H NMR (300 MHz, CDCl3, mixture of rotamers) δ 4.83 (m, 1H), 3.95 (m, 1H), 3.47 (m, 1H), 2.68 (m, 2H), 1.54 (m, 2H), 1.31 (s, 2H), 0.87 (s, 3H). MS (EI) m/z (rel %) 207 [M+H]+ (5), 180 (5), 130 (30), 111 (70), 95 (100), 79 (90), 64 (100). HRMS (EI) calcd for C5H11NO2Si [M+H]+ 206.0777, found 206.0775.

(−)-(55,65,7aS)-5-Azido-5,6,7,7a-tetrahydro-6-(trisopropylsilyloxy)-2,2-oxocyclohexyl (Diethylphosphono)acetate (24). To a solution of phosphonate (1) (1.40 g, 2.76 mmol) in DCM (15 mL) at 0 °C was slowly added a solution of Dess–Martin periodinane (2.30 g, 5.52 mmol) in DCM (13 mL). The solution was stirred for 2 h at 0 °C and 1 h at rt. Saturated aq NaHCO3 was added, and the mixture was vigorously stirred for 1 h at rt. The usual workup (DCM, H2O) and purification (50% EtOAc in hexanes) gave 24 (1.16 g, 85%) as a colorless oil: [α]D22 +8.98 (c 1.66, CHCl3); IR (film) ν 2948, 2869, 2114, 1743, 1560, 1456, 1270, 1101, 1027, 966, 882, 633 cm−1. 1H NMR (300 MHz, CDCl3) δ 5.66 (dd, J = 12.3, 6.9 Hz, 1H), 4.26–4.09 (m, 6H), 3.18–2.98 (m, 3H), 2.64–2.56 (m, 1H), 2.37–2.18 (m, 2H), 2.13 (dt, J = 7.1, 1.8 Hz, 6H), 1.22–1.00 (m, 21H); 13C NMR (100 MHz, CDCl3) δ 200.1 (s), 164.5 (d, JDC1−C2 = 5.8 Hz), 73.2 (d), 68.4 (d), 64.1 (d), 62.7 (td, JDC1−C2 = 6.3 Hz), 62.5 (td, JDC1−C2 = 6.3 Hz), 39.7 (t), 35.0 (t), 33.7 (td, JDC1−C2 = 134.6 Hz), 17.8 (q), 16.2 (qd, JDC1−C2 = 6.2 Hz), 16.1 (q), 11.9 (d); MS (EI) m/z (rel %) 462 [M−C6H10N3O2]+ (21), 391 (100), 281 (30), 235 (45), 179 (15), 151 (31), 123 (20). 1H NMR of the crude mixture was stirred for 2 h at rt and then concentrated under reduced pressure. DCM was added, and the organic layer was washed twice with aq NaOH (1 N). The usual workup (DCM) and purification (30% to 50% EtOAc in hexanes) gave 21 (524 mg, 73%) as a yellow oil: [α]D22 +7.00 (c 1.12, CHCl3); IR (film) ν 3282 (br), 2949, 2870, 1761, 1671, 1462, 1394, 1098, 1080, 1001, 980, 881 cm−1. 1H NMR (300 MHz, CDCl3, mixture of rotamers) δ 8.25 (s) and 8.17 (s) (1H, rotamers), 5.92 (s, 1H), 5.23 (dd, J = 12.0, 6.9 Hz, 1H), 4.60–4.53 (m, 4.37, 4.37, 4.28 (br) s and 4.03–3.96 (m) (2H, rotamer), 4.55 (qd, J = 12.0, 6.9 Hz, 1H), 4.33–4.34 (m, 3.10 (m), 2.99 (br) and 2.97 (br s) (4H, rotamers), 2.67–2.39 (m, 3H), 2.13 (t, J = 2.6 Hz) and 2.02 (t, J = 2.7 Hz) (1H, rotamers), 1.70–1.46 (m, 1H), 1.25–1.02 (m, 21H); 13C NMR (100 MHz, CDCl3, mixture of rotamers) δ 172.7 (s), 172.2 (s), 169.5 (s), 168.2 (s), 164.4 (d), 161.8 (d), 114.8 (d), 114.3 (d), 81.2 (s), 78.6 (d), 78.1 (d), 72.6 (d), 70.5 (d), 69.5 (d), 68.6 (d), 60.4 (d), 56.4 (d), 43.7 (t), 43.7 (t), 35.9 (t), 35.9 (t), 34.3 (t), 28.0 (t), 25.9 (t), 22.2 (t), 18.1 (q), 17.7 (t), 12.1 (d); MS (EI) m/z (rel %) 362 [M−C3H8]+ (100), 294 (210), 210 (70), 74 (20). HRMS (EI) calcd for C21H31NO3Si [M−C3H8]+ 362.1787, found 362.1792.
A ring should be a piperidine, not a pyrrolidine. It should be noted that the structure of securinol A drawn in this article is erroneous: to be consistent with data and discussion in this article, the A ring should be a piperidine, not a pyrrolidine.

The authors declare no competing financial interest.

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(3) Wang, G.-C.; Wang, Y.; Li, Q.; Liang, J.-P.; Zhang, X.-Q.; Yao, X.-S.; Ye, W.-C. Helv. Chim. Acta 2008, 91, 1124–1128. It should be noted that the structure of securinol A drawn in this article is erroneous: to be consistent with data and discussion in this article, the A ring should be a piperidine, not a pyrrolidine.
(11) The enantiomeric ratio was determined by gas chromatography. See Experimental Section.
(13) Other bases (KHMDS, DIPEA, NaH), additives (LiCl, 18-crown-6 ether), solvents (MeCN, PhMe), and temperatures (−40, 0 °C) were screened without yield improvement.
(14) Lowering the amount of triflic anhydride and/or tetrabutylphosphonium bromide and/or base, using other solvents or solvent mixtures, and increasing the reaction time or temperature for either the Vilsmeier–Haack or the Mannich cyclizations all resulted in lower yields, often as the result of extensive decomposition of the iminium intermediate obtained after the Vilsmeier–Haack cyclization.
(15) The estimated enantiomeric ratio of this compound is 96:4 on the enantiomeric ratio of compound (+)-22 from which it is derived.