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

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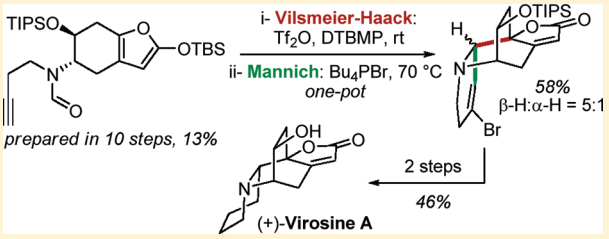
Supporting Information

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[1] and are known to act on the central nervous system as γ-aminobutyric acid (GABA) receptor antagonists.[2] 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).

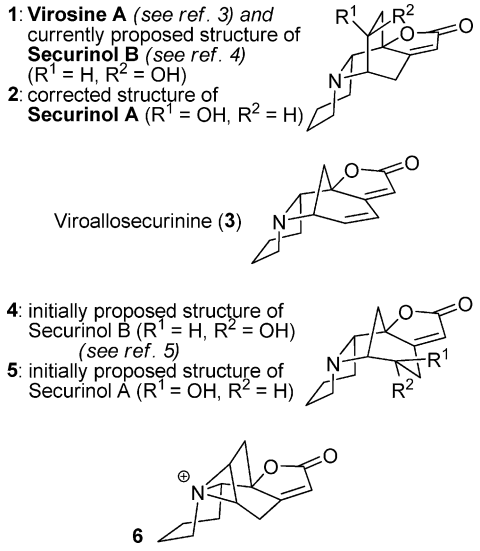


Figure 1. Representative *Securinega* alkaloids.

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[3.2.1]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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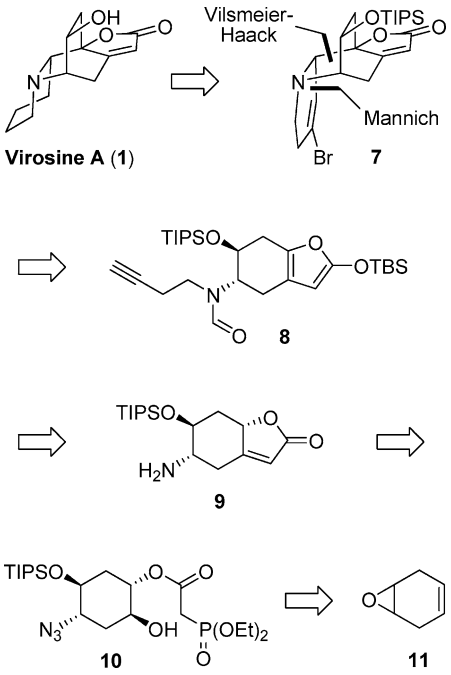
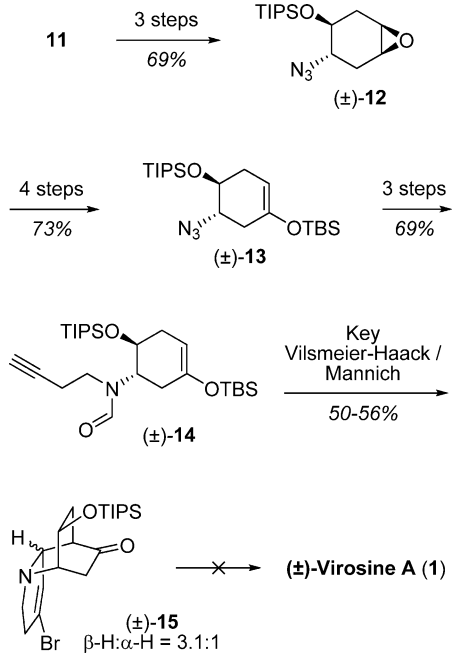
Scheme 1. Retrosynthetic Analysis of Virosine A



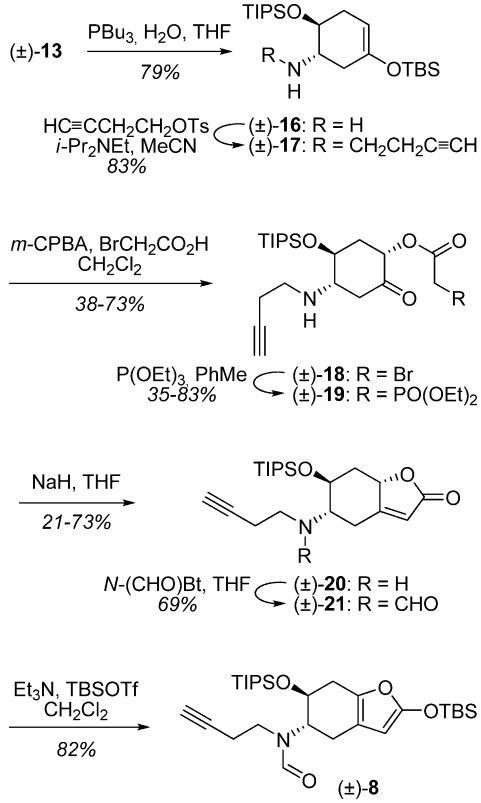
We already have disclosed our approach to the core of virosine A (securinol B) (Scheme 2).[8] In this first generation approach, we demonstrated the viability of the key Vilsmeier–Haack/Mannich cyclizations to generate a tricyclic product **15** in a racemic form. Only 11 steps were required to access this advanced intermediate. Unfortunately, all attempts to install the butenolide ring of virosine A from **15** failed.

Scheme 2. First Generation Approach towards the Core of (±)-Virosine A



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.[9] In a second generation approach (Scheme 3), the furyl was installed from intermediate **13**

Scheme 3. Second Generation Approach towards (±)-Virosine A



common to the first generation approach. After a Staudinger type reduction of the azide, amine **16**[8] was alkylated with a homopropargylic tosylate. The steric hindrance generated by the adjacent OTIPS group prevented the bis-alkylation of the amine, which is often problematic with less congested primary amines. Rubottom oxidation of enol ether **17** in the presence of bromoacetic acid then afforded bromoacetate **18** as a single diastereomer and regioisomer. The butenolide ring was installed by aid of an Arbuzov reaction with triethylphosphite and a subsequent intramolecular Horner–Wadsworth–Emmons olefination. Formylation of amine **20** with *N*-formylbenzotriazole[10] followed by enolization of the butenolide **21** produced the key step precursor **8**. Even though the furyl group could be successfully installed this way, this route was not optimal since three steps (from **17** to **20**) showed reproducibility issues (cf. yield ranges).

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),[11] which compares to literature.[12] 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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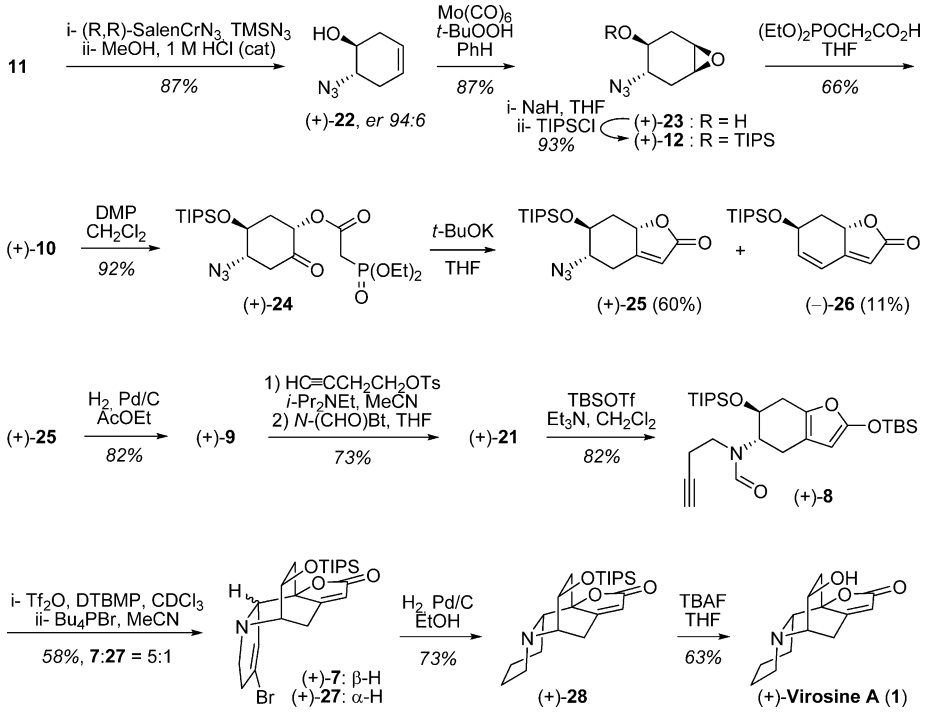
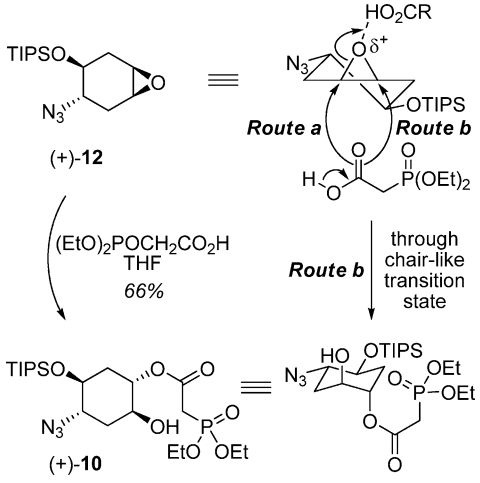
Scheme 4. Third Generation Approach: Total Synthesis of (+)-Virosine A



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

Scheme 5. Diastereoselectivity in Epoxide 12 Opening



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 N_3 elimination from **25**.[13] 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 optimized[14] 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

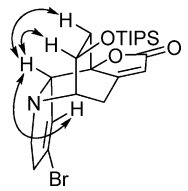


Figure 2. NOESY interactions for compound (+)-7.

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 TIPS ether finally afforded virosine A. The characterization of the synthetic material matched that for the isolated natural product.[3]

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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 deducted by Ye[3] for virosine A. Even though the revised structure proposed by Arbain and Sargent[4] for securinol B is exactly the same as for virosine A, the absence of spectral data for the former do 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, diisopropylethylamine, and triethylamine were distilled from CaH_2 under nitrogen immediately prior to use. Methanol was distilled over 4 Å molecular sieves. Triflic anhydride and $CDCl_3$ were distilled over a small amount of phosphorus pentoxide (P_2O_5) under nitrogen immediately prior to use. Azidotrimethylsilane and *tert*-butyldimethylsilyl trifluoromethanesulfonate were distilled under nitrogen immediately prior to use. *p*-Toluenesulfonyl chloride was recrystallized in benzene prior to use. All other required fine chemicals were used directly without purification. Thin layer chromatography (TLC) was conducted with precoated 60 Å 250 μm silica gel plates with F-254 indicator and visualized using a combination of UV and anisaldehyde, ceric ammonium molybdate, iodine on silica, or potassium permanganate staining. Flash column chtomatography was performed using silica gel (230–400 mesh). Melting points are uncorrected. Optical rotations were measured at rt in a 1.0 dm cell (c in g cm^{-3}). IR spectra were recorded with a FTIR instrument by applying substrates as thin films onto a KBr plate. ^{1}H and ^{13}C NMR spectra were recorded on 300 MHz and/or 400 MHz spectrometers. All chemical shifts are referenced to residual non-deutarated solvent. Data for proton spectra are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and multiplet (m)], coupling constants [Hz], integration). Carbon spectra were recorded with complete proton decoupling and the chemical shifts are reported in ppm.

Usual Reaction Workup and Purification. After addition of the indicated aqueous solution, layers were separated. The aqueous phase was extracted with the indicated solvent and washed with the indicated aqueous solution. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure using a rotary evaporator. The crude material was purified by flash chromatography using silica gel with the indicated eluent.

(+)-Virosine A (1). To a solution of **28** (4.0 mg, 0.010 mmol) in THF (0.2 mL) at 0 °C was added tetrabutylammonium fluoride (1.0 M in THF, 11 μL, 0.011 mmol). The reaction mixture was stirred at rt for 20 min. Aqueous NaOH (1 N) and EtOAc were added, and layers were separated. The aqueous phase was extracted with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, 85% EtOAc in hexanes) to give virosine A (**1**) (1.5 mg, 63%) as an oily solid. $[\alpha]^{20}_D$ +22.8 (c 0.35, 1,4-dioxane);[15] IR (film) ν 3394 (br), 2926, 2851, 1755, 1728, 1653, 1597, 1454, 1143 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (s, 1H), 4.43–4.34 (m, 1H), 3.02–2.86 (m, 3H), 2.85–2.66 (m, 4H), 1.87–1.76 (m, 1H), 1.74–1.51 (m, 4H), 1.46 (dd, J = 12.4, 5.0 Hz, 1H), 1.38–1.26 (m, 1H), 0.86 (qd, J = 11.8, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 (s), 173.9 (s), 111.8 (d), 84.5 (s), 65.5 (d), 65.3 (d), 59.1 (d), 52.9 (t), 41.1 (t), 29.6 (t), 26.8 (t), 25.8 (t), 24.2 (t); MS (EI) m/z (rel %) 235 [M$^+$] (60), 191 (100), 163 (15), 149 (20), 140 (45), 110 (55), 84 (30); HRMS (EI) calcd for $C_{13}H_{17}NO_3$ [M$^+$] 235.1208, found 235.1210.

(+)-(1*S*,2*R*,8*S*,15*S*)-7-Aza-4-bromo-13-oxa-15-(triisopropylsilyloxy)tetracyclo[6.5.2.0.^{2,7}0^{1,10}]pentadeca-3,10-dien-12-one (7) and (+)-(1*S*,2*S*,8*S*,15*S*)-7-Aza-4-bromo-13-oxa-15-(triisopropylsi-lyloxy)tetracyclo[6.5.2.0.^{2,7}0^{1,10}]pentadeca-3,10-dien-12-one (27). Triflic anhydride (15 μL, 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 $CDCl_3$ (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 Na_2CO_3 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 Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel saturated with Et_3N, 0% to 15% EtOAc in hexanes) to give **7** (13 mg, 48%) and **27** (2.8 mg, 10%).

Data for **7**: beige solid, mp 82–84 °C; $[\alpha]^{20}_D$ +33.0 (c 0.54, $CHCl_3$);[15] IR (film) ν 2937, 2866, 1788, 1769, 1653, 1465, 1140, 1053, 877 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85, (br. s, 1H), 5.75 (br. s, 1H), 4.33 (dd, J = 8.0, 4.9 Hz, 1H), 3.99–3.94 (m, 1H), 3.31–3.16 (m, 2H), 3.10 (dd, J = 14.3, 5.4 Hz, 1H), 2.99–2.93 (m, 1H), 2.76 (dd, J = 12.9, 8.5 Hz, 1H), 2.68–2.48 (m, 2H), 2.32–2.21 (m, 1H), 1.50 (d, J = 13.1 Hz, 1H), 1.13–0.96 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4 (s), 172.3 (s), 127.6 (d), 122.7 (s), 112.0 (d), 84.8 (s), 67.3 (d), 59.2 (d), 58.8 (d), 49.7 (t), 42.5 (t), 34.1 (t), 27.2 (t), 18.1 (q), 12.1 (d); MS (ESI) m/z (rel %) 470 and 468 [M$^+$] (100), 414 (10), 227 (10), 196 (10); HRMS (ESI) calcd for $C_{22}H_{34}BrNO_3Si$ [M$^+$] 468.1570, found 468.1571.

Data for **27**: oily solid. $[\alpha]^{20}_D$ +16.7 (c 0.29, $CHCl_3$);[15] IR (film) ν 2945, 2926, 2866, 1776, 1758, 1653, 1465, 1128, 1053, 881, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (br. s, 1H), 5.75 (br. s, 1H), 4.27–4.18 (m, 1H), 3.55 (br. s, 1H), 3.29–3.10 (m, 2H), 3.04 (dd, J = 14.6, 4.9 Hz, 1H), 2.99–2.94 (m, 1H), 2.92–2.81 (m, 1H), 2.69 (dd, J = 13.0, 9.4 Hz, 1H), 2.57–2.42 (m, 1H), 2.42–2.31 (m, 1H), 1.37–1.29 (m, 1H), 1.12–0.96 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3 (s), 173.5 (s), 128.8 (d), 122.3 (s), 111.5 (d), 84.6 (s), 67.1 (d), 61.4 (d), 61.1 (d), 49.1 (t), 36.7 (t), 35.1 (t), 29.0 (t), 18.2 (q), 12.2 (d); MS (ESI) m/z (rel %) 490 [M$^+$ + Na] (95), 446 (30), 393 (15), 349 (20), 301 (25), 289 (20), 202 (15); HRMS (ESI) calcd for $C_{22}H_{34}BrNNaO_3Si$ [M$^+$ + Na] 490.1389, found 490.1389.

(+)-*N*-(But-3-ynyl)-*N*-((5*S*,6*S*)-4,5,6,7-tetrahydro-2-(*tert*-butyldimethylsilyloxy)-6-(triisopropylsilyloxy)benzofuran-5-yl)-formamide (8). To a solution of butenolide **21** (19 mg, 0.047 mmol) and Et_3N (34 μL, 0.24 mmol) in DCM (0.5 mL) at 0 °C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (28 μL, 0.12 mmol). Saturated aq Na_2CO_3 was immediately added. The usual workup (DCM) and purification (silica gel saturated with Et_3N, 30% EtOAc in hexanes) gave **8** (20 mg, 82%) as a colorless oil: $[\alpha]^{20}_D$ +34.8 (c 0.85, $CHCl_3$);[15] IR (film) ν 3316, 2945, 2892, 2866, 1683, 1597, 1462, 1271, 1256, 1095, 885, 844 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 8.19 (s) and 8.14 (s) (1H, rotamers), 4.92 (s) and 4.89 (s) (1H, rotamers), 4.87–4.77 (m) and 4.23–4.13 (m) (1H, rotamers), 3.69–3.33 (m, 2H), 3.33–3.19 (m, 1H), 3.02 (td, J = 16.1, 5.7 Hz, 1H), 2.76–2.34 (m, 5H), 2.06 (t, J = 2.5 Hz) and 2.01 (t, J = 2.5 Hz) (1H, rotamers), 1.08–1.03 (m, 21H), 0.98–0.94 (m, 9H), 0.24–0.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers) δ 163.9 (d), 163.7 (d), 156.7 (s), 156.3 (s), 135.5 (s), 135.1 (s), 116.0 (s), 115.2 (s), 84.0 (d), 83.8 (d), 81.6 (s), 80.5 (s), 71.4 (d), 70.1 (d), 69.2 (d), 68.1 (d), 61.5 (d), 60.6 (d), 49.2 (t), 42.1 (t), 33.4 (t), 32.8 (t), 26.5 (t), 25.6 (q), 24.1 (t), 20.4 (t), 18.6 (t), 18.3 (q), 18.2 (s), 13.0 (d), 12.9 (d), −4.8 (q); MS (EI) m/z (rel %) 519 [M$^+$] (40), 476 [M$^+$ − C_3H_7] (35), 422 (50), 248 (80), 224 (100), 210 (15), 73 (55); HRMS (EI) calcd for $C_{28}H_{49}NO_4Si_2$ [M$^+$] 519.3200, found 519.3193.

(+)-(5*S*,6*S*,7a*S*)-5-Amino-5,6,7,7a-tetrahydro-6-(triisopropylsilyloxy)benzofuran-2(4*H*)-one (9). To a solution of azide **25** (754 mg, 2.14 mmol) in EtOAc (20 mL) at rt was added palladium on carbon (10 wt %, 223 mg). The reaction mixture was stirred for 2 h at rt under hydrogen atmosphere. The solution was filtered on Celite (EtOAc washings). The solvent was evaporated

under reduced pressure, and the usual purification (10% MeOH in EtOAc) gave **9** (573 mg, 82%) as a white solid: mp 61−64 °C; $[\alpha]^{20}_{D}$ +57.7 (*c* 0.80, $CHCl_3$);[15] IR ($CHCl_3$) ν 3686, 3623, 3023, 2971, 2870, 1750, 1522, 1428, 1215, 1035, 930 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (s, 1H), 5.08 (dd, *J* = 11.0, 6.4 Hz, 1H), 4.09−4.00 (m, 1H), 3.42−3.36 (m, 1H), 3.02 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.61 (d, *J* = 13.8 Hz, 1H), 2.57−2.47 (m, 1H), 1.76−1.65 (m, 1H), 1.55 (s, 2H), 1.18−1.01 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4 (s), 169.4 (s), 115.6 (d), 79.2 (d), 71.9 (d), 53.6 (d), 36.1 (t), 31.9 (t), 18.2 (q), 12.3 (d); MS (EI) *m*/*z* (rel %) 308 (5), 282 [$M^+ - C_3H_7$] (100), 184 (2), 130 (10), 102 (5); HRMS (EI) calcd for $C_{14}H_{24}NO_3Si$ [$M^+ - C_3H_7$] 282.1525, found 282.1527.

(+)-(1*S*,2*S*,4*S*,5*S*)-4-Azido-2-hydroxy-5-(triisopropylsilyloxy)-cyclohexyl (diethylphosphono)acetate (10). To a solution of epoxide **12** (2.42 g, 7.77 mmol) in THF (78 mL) was added diethylphosphonoacetic acid (25.0 mL, 155 mmol). The solution was stirred for 15 h at 70 °C. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in EtOAc and washed three times with saturated aq $NaHCO_3$. The usual workup (EtOAc, H_2O) and purification (50% EtOAc in hexanes) gave **10** (2.60 g, 66%) as a colorless oil: $[\alpha]^{20}_{D}$ +38.5 (*c* 1.11, $CHCl_3$);[15] IR (film) ν 3377, 2944, 2869, 2109, 1734, 1646, 1557, 1465, 1390, 1266, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.11 (ddd, *J* = 11.5, 9.1, 4.6 Hz, 1H), 4.40 (s, 1H), 4.23−4.10 (m, 4H), 4.05−3.99 (m, 1H), 3.93−3.82 (m, 1H), 3.82−3.77 (m, 1H), 3.12−2.81 (m, 2H), 2.16−1.97 (m, 3H), 1.84−1.72 (m, 1H), 1.35 (dd, *J* = 13.2, 6.9 Hz, 6H), 1.18−0.98 (m, 21H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.2 (d, $J_{^{13}C-^{31}P}$ = 5.5 Hz), 75.9 (d), 69.4 (d), 67.7 (d), 63.3 (td, $J_{^{13}C-^{31}P}$ = 5.8 Hz), 62.8 (td, $J_{^{13}C-^{31}P}$ = 6.3 Hz), 62.0 (d), 35.0 (td, $J_{^{13}C-^{31}P}$ = 130.6 Hz), 32.7 (t), 30.8 (t), 17.9 (q), 16.3 (qd, $J_{^{13}C-^{31}P}$ = 4.9 Hz), 12.1 (d); MS (EI) *m*/*z* (rel %) 464 [$M^+ - C_3H_7$] (60), 309 (5), 281 (5), 240 (100), 222 (65), 179 (30), 123 (30); HRMS (EI) calcd for $C_{18}H_{35}N_3O_7PSi$ [$M^+ - C_3H_7$] 464.1982, found 464.1993.

(+)-((1*R*,3*S*,4*S*,6*S*)-4-Azido-7-oxabicyclo[4.1.0]heptan-3-yloxy)triisopropylsilane (12). Sodium hydride (60% in mineral oil, 1.88 g, 47.1 mmol) was added to a solution of alcohol **23** (6.09 g, 39.3 mmol) in THF (250 mL) at 0 °C. The resulting mixture was stirred at rt for 1.5 h, TIPSCl was added at 0 °C, and the reaction mixture was stirred at rt for 18 h. Water was added carefully, and the reaction mixture was concentrated under reduced pressure. The usual workup (EtOAc, brine) and purification (2% to 10% EtOAc in hexanes) gave **12** (11.2 g, 93%) as a light brown oil: $[\alpha]^{20}_{D}$ +11.1 (*c* 1.24, $CHCl_3$);[15] IR (film) ν 2940, 2105, 1465, 1256, 1110, 818, 681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.64 (td, *J* = 10.0, 7.0 Hz, 1H), 3.40 (ddd, *J* = 11.0, 10.0, 5.0 Hz, 1H), 3.17 (dt, *J* = 4.0, 2.0 Hz, 1H), 3.08 (dd, *J* = 5.0, 4.0 Hz, 1H), 2.50 (ddd, *J* = 15.0, 5.0, 2.0 Hz, 1H), 2.40 (ddd, *J* = 15.0, 7.0, 5.0 Hz, 1H), 1.98 (dd, *J* = 15.0, 10.0 Hz, 1H), 1.67 (ddd, *J* = 15.0, 11.0, 2.0 Hz, 1H), 1.15−0.99 (m, 21H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 71.2 (d), 61.4 (d), 52.3 (d), 50.5 (d), 34.1 (t), 30.4 (t), 18.0 (q), 12.7 (d); MS (CI) *m*/*z* (rel %) 312 [M^+ + H] (100), 240 (20); HRMS (CI) calcd for $C_{15}H_{30}N_3O_2Si$ [M^+ + H] 312.2107, found 312.2120.

But-3-ynyl *p*-Toluenesulfonate. To a solution of but-3-yn-1-ol (1.20 mL, 15.8 mmol), triethylamine (2.70 mL, 19.0 mmol), and 4-(dimethylamino)pyridine (39 mg, 0.32 mmol) in DCM (53 mL) at 0 °C was added *p*-toluenesulfonyl chloride (3.16 g, 16.6 mmol) in three portions. The reaction mixture was brought to rt and stirred 15 h. Aq NaOH (1 N, 30 mL) was added, and the mixture was vigorously stirred for 15 min at rt. The usual workup (DCM, brine) gave but-3-ynyl *p*-toluenesulfonate (3.46 g, 98%) as a yellowish oil. The product obtained is in agreement with published spectra:[17] ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 4.10 (t, *J* = 7.1 Hz, 2H), 2.56 (td, *J* = 7.1, 2.7 Hz, 2H), 2.46 (s, 3H), 1.97 (t, *J* = 2.7 Hz, 1H).

***rac*-*N*-(But-3-ynyl)-*N*-((1*S*,6*S*)-3-(*tert*-butyldimethylsilyloxy)-6-(triisopropylsilyloxy)cyclohex-3-enylamine (17).** A solution of but-3-ynyl *p*-toluenesulfonate (2.27 g, 10.1 mmol) in MeCN (30 mL) was added to a solution of amine **16**[8] (2.02 g, 5.06 mmol) and *N*,*N*-diisopropylethylamine (1.90 mL, 11.1 mmol) in MeCN (20 mL) at rt. The reaction mixture was stirred for 15 h at 70 °C. Saturated aq $NaHCO_3$ and EtOAc were added. The usual workup (EtOAc, brine) and purification (silica gel saturated with Et_3N, 5% EtOAc in hexanes) gave **17** (2.02 g, 88%) as a colorless oil: IR (film) ν 3314, 2933, 2869, 1676, 1464, 1252, 1194, 1098, 886, 839, 780, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.72−4.66 (m, 1H), 3.80 (td, *J* = 8.1, 5.3 Hz, 1H), 2.91−2.64 (m, 3H), 2.43−2.28 (m, 4H), 2.16−2.02 (m, 2H), 2.00−1.86 (m, 1H), 1.09−1.04 (m, 21H), 0.91 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.2 (s), 100.7 (d), 82.6 (s), 71.4 (d), 69.6 (d), 58.8 (d), 45.8 (t), 34.8 (t), 31.8 (t), 25.8 (q), 19.8 (t), 18.3 (q), 18.1 (s), 12.7 (d), −4.4 (q); MS (EI) *m*/*z* (rel %) 451 [M^+] (15), 408 [$M^+ - C_3H_7$] (30), 371 (30), 278 (100), 256 (70), 210 (25); HRMS (EI) calcd for $C_{25}H_{49}NO_2Si_2$ [M^+] 451.3302, found 451.3304.

***rac*-(1*S*,4*S*,5*S*)-4-(But-3-ynylamino)-5-(triisopropylsilyloxy)-2-oxocyclohexyl Bromoacetate (18).** Bromoacetic acid (3.50 g, 25.5 mmol) was added to a solution of *m*-chloroperbenzoic acid (77%, 372 mg, 1.66 mmol) in DCM (3.5 mL) at −25 °C. A solution of amine **17** (500 mg, 1.11 mmol) in DCM (3 mL) was added over 1 h, and the solution was stirred for 30 min at −25 °C. Saturated aq Na_2SO_3 was added, and the mixture was stirred for 30 min at rt. Aqueous NaOH (1 N) was added. The usual workup (DCM) and purification (20% EtOAc in hexanes) gave **18** (single diastereomer, 383 mg, 73%) as a yellowish oil: IR (film) ν 3752, 3734, 2944, 2869, 2335, 1734, 1650, 1562, 1504, 1465, 1275, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.55 (dd, *J* = 12.2, 6.9 Hz, 1H), 4.23−4.17 (m, 1H), 3.96 (s, 2H), 3.33−3.27 (m, 1H), 3.08 (dd, *J* = 13.8, 4.0 Hz, 1H), 2.84−2.64 (m, 2H), 2.46−2.23 (m, 6H), 1.22−1.00 (m, 21H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 203.0 (s), 166.4 (s), 81.9 (s), 74.8 (d), 70.2 (d), 69.2 (d), 61.6 (d), 45.4 (t), 41.2 (t), 35.5 (t), 25.9 (t), 19.6 (t), 18.2 (q), 12.3 (d); MS (EI) *m*/*z* (rel %) 432 and 430 [$M^+ - C_3H_7$] (20), 317 (70), 278 (100), 253 (25), 241 (35), 223 (20), 131 (20); HRMS (EI) calcd for $C_{18}H_{29}BrNO_4Si$ [$M^+ - C_3H_7$] 430.1049, found 430.1054.

***rac*-(1*S*,4*S*,5*S*)-4-(But-3-ynylamino)-5-(triisopropylsilyloxy)-2-oxocyclohexyl (Diethylphosphono)acetate (19).** To a solution of bromide **18** (252 mg, 0.531 mmol) in toluene (11 mL) was added triethylphosphite (1.4 mL, 8.0 mmol) at rt. The reaction mixture was stirred for 3 h at reflux. Solvent and excess triethylphosphite were evaporated under reduced pressure. The usual purification (50% to 85% EtOAc in hexanes) gave **19** (253 mg, 90%) as a colorless oil: IR (film) ν 3297, 2945, 2870, 1754, 1735, 1638, 1465, 1391, 1267, 1106, 1053, 1024, 971, 881 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.54 (dd, *J* = 12.2, 6.8 Hz, 1H), 4.26−4.12 (m, 5H), 3.33−3.26 (m, 1H), 3.18−2.98 (m, 3H), 2.83−2.64 (m, 2H), 2.46−2.22 (m, 6H), 1.34 (td, *J* = 7.1, 1.2 Hz, 6H), 1.21−1.01 (m, 21H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 203.1 (s), 164.9 (d, $J_{^{13}C-^{31}P}$ = 4.4 Hz), 81.9 (s), 74.1 (d), 70.1 (d), 69.2 (d), 63.7 (td, $J_{^{13}C-^{31}P}$ = 3.9 Hz), 62.8 (td, $J_{^{13}C-^{31}P}$ = 6.7 Hz), 61.7 (d), 45.3 (t), 41.2 (t), 35.6 (t), 34.0 (td, $J_{^{13}C-^{31}P}$ = 134.8 Hz), 19.6 (t), 18.2 (q), 16.4 (qd, $J_{^{13}C-^{31}P}$ = 5.2 Hz), 12.3 (d); MS (EI) *m*/*z* (rel %) 531 [M^+] (10), 492 [$M^+ - C_3H_3$] (20), 488 [$M^+ - C_3H_7$] (50), 331 (40), 313 (60), 153 (100); HRMS (EI) calcd for $C_{25}H_{46}NO_7PSi$ [M^+] 531.2781, found 531.2787.

***rac*-(5*S*,6*S*,7a*S*)-5-(But-3-ynylamino)-5,6,7,7a-tetrahydro-6-(triisopropylsilyloxy)benzofuran-2(4*H*)-one (20).** To a suspension of sodium hydride (60% dispersion in mineral oil, 7.7 mg, 0.19 mmol) in THF (0.6 mL) at −40 °C was added a solution of phosphonate **19** (92.4 mg, 0.174 mmol) in THF (0.6 mL). The reaction mixture was stirred for 2 h at −40 °C. Brine and Et_2O were added. The usual workup (Et_2O, H_2O) and purification (30% EtOAc in hexanes) gave **20** (47.7 mg, 73%) as a white solid: mp 34−36 °C; IR ($CHCl_3$) ν 3690, 3626, 3308, 3023, 2975, 2870, 1746, 1525, 1424, 1215, 1042, 922, 788 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (s, 1H), 5.06 (dd, *J* = 11.2, 6.3 Hz, 1H), 4.20−4.13 (m, 1H), 3.15−3.09 (m, 1H), 2.98−2.87 (m, 1H), 2.86−2.67 (m, 3H), 2.56−2.45 (m, 1H), 2.38−2.29 (m, 2H), 2.00 (t, *J* = 2.5 Hz, 1H), 1.76−1.64 (m, 1H), 1.18−1.00 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (s), 169.7 (s), 115.1 (d), 82.1 (s), 79.1 (d), 70.2 (d), 69.8 (d), 59.5 (d), 45.9 (t), 36.5 (t), 29.0 (t), 19.9 (t), 18.2 (q), 12.3 (d); MS (EI) *m*/*z* (rel %) 377 [M^+] (15), 338 [$M^+ - C_3H_3$] (15), 334 [$M^+ - C_3H_7$] (100), 280 (20), 73 (40); HRMS (EI) calcd for $C_{21}H_{35}NO_3Si$ [M^+] 377.2386, found 377.2382.

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(+)-*N*-(But-3-ynyl)-*N*-((5*S*,6*S*,7a*S*)-2,4,5,6,7,7a-hexahydro-6-triisopropylsilyloxy-2-oxobenzofuran-5-yl)formamide (21). Preparation from **20**: To a solution of butenolide **20** (15.9 mg, 0.042 mmol) in THF (2.1 mL) was added *N*-formylbenzotriazole[10] (49.6 mg, 0.34 mmol) at rt. The reaction mixture was stirred for 15 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, brine) and purification (30% EtOAc in hexanes) gave **21** (11.8 mg, 69%) as a yellowish oil. Preparation from **9**: A solution of but-3-ynyl *p*-toluenesulfonate (2.38 g, 10.6 mmol) in MeCN (9 mL) was added to a solution of amine **9** (574 mg, 1.76 mmol) and *N*,*N*-diisopropylethylamine (0.6 mL, 3.52 mmol) in MeCN (9 mL) at rt. The reaction mixture was stirred for 60 h at 70 °C. Saturated aq $NaHCO_3$ and EtOAc were added. After the usual workup (EtOAc, brine), the residue was dissolved in THF (88 mL), and *N*-formylbenzotriazole[10] (2.07 g, 14.1 mmol) was added at rt. The reaction mixture was stirred for 72 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 yellowish oil: $[\alpha]^{20}_D$ +70.0 (*c* 1.12, $CHCl_3$);[15] IR (film) ν 3282 (br.), 2949, 2870, 1761, 1671, 1462, 1394, 1098, 1080, 1001, 900, 881 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 8.25 (s) and 8.17 (s) (1H, rotamers), 5.92 (s, 1H), 5.23 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.60−4.53 (m), 4.37 (br. s), 4.28 (br. s) and 4.03−3.96 (m) (2H, rotamers), 3.76−3.64 (m), 3.44−3.35 (m), 3.28−3.10 (m), 3.02 (br. s) 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); ^{13}C NMR (100 MHz, $CDCl_3$, 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), 54.6 (d), 43.7 (t), 43.6 (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 [$M^+ - C_3H_7$] (100), 294 (5), 210 (5), 74 (20); HRMS (EI) calcd for $C_{19}H_{28}NO_4Si$ [$M^+ - C_3H_7$] 362.1787, found 362.1782.

(+)-(1*S*,6*S*)-6-Azidocyclohex-3-enol (22). Nitrogen was bubbled in epoxide **11** (1.95 g, 20.3 mmol) for 10 min, and it was then brought to −25 °C. (*R*,*R*)-SalenCrN_3[12,18] (975 mg, 1.52 mmol) and azidotrimethylsilane (2.80 mL, 21.3 mmol) were added, and the reaction mixture was stirred at −25 °C for 5 days. The mixture was filtered on a silica pad, eluting with a mixture of 15% EtOAc in hexanes. The filtrate was concentrated under reduced pressure and then diluted in methanol (70 mL). Aqueous 1 N HCl (5 drops) was added. The resulting mixture was stirred 1 h at rt, concentrated under reduced pressure, and then diluted in DCM. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The usual purification (10% EtOAc in hexanes) gave **22** (2.47 g, 87%) as a yellowish oil: er 94:6 (GC, RT-BetaDexsp column, 30 m × 0.25 mm × 0.25 μm); $[\alpha]^{20}_D$ +100.0 (*c* 1.25, $CHCl_3$); IR (film) ν 3402 (br), 3035, 2914, 2108, 1658, 1254, 1062, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.64−5.54 (m, 2H), 3.74 (tdd, *J* = 9.0, 6.0, 3.0 Hz, 1H), 3.55 (dt, *J* = 9.0, 6.0 Hz, 1H), 2.59−2.47 (m, 2H), 2.26 (d, *J* = 3.0 Hz, 1H), 2.22−2.05 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 124.4 (d), 123.2 (d), 69.8 (d), 63.0 (d), 32.8 (t), 30.0 (t); MS (EI) *m*/*z* (rel %) 139 [M^+] (1), 94 (45), 83 (50), 55 (100); HRMS (EI) calcd for $C_6H_9N_3O$ [M^+] 139.0746, found 139.0748.

(+)-(1*R*,3*S*,4*S*,6*S*)-4-Azido-7-oxabicyclo[4.1.0]heptan-3-ol (23). A solution of anhydrous *tert*-butyl hydroperoxide[19] (2.30 M in toluene, 41.8 mL, 96.1 mmol) was added over 5 min to a solution of alkene **22** (6.08 g, 43.7 mmol) and $Mo(CO)_6$ (0.58 g, 2.2 mmol) in benzene (300 mL) at reflux. After 2 h at reflux, the reaction mixture was cooled to 0 °C and quenched by carefully adding saturated aq $Na_2S_2O_3$. Water was added, and the usual workup (EtOAc, brine) and purification (40% EtOAc in hexanes) gave **23** (5.90 g, 87%) as a white solid: mp 59−61 °C; $[\alpha]^{20}_D$ +61.6 (*c* 1.02, $CHCl_3$);[15] IR (film) ν 3327 (br), 3012, 2924, 2118, 1436, 1256, 1065, 953, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.63−3.54 (m, 2H), 3.27−3.24 (m, 1H), 3.22 (t, *J* = 4.0 Hz, 1H), 2.59−2.58 (m, 1H), 2.54 (dd, *J* = 4.0, 1.0 Hz, 1H), 2.37 (ddd, *J* = 16.0, 5.5, 4.0 Hz, 1H), 2.06 (dd, *J* = 16.0, 7.0 Hz, 1H), 1.98−1.89 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 68.5 (d), 59.7 (d), 51.8 (d), 51.2 (d), 30.0 (t), 28.0 (t); MS (CI) *m*/*z* (rel %) 156 [M^+ + H] (35), 113 (50), 98 (75), 82 (100); HRMS (CI) calcd for $C_6H_{10}N_3O_2$ [M^+ + H] 156.0773, found 156.0777.

(+)-(1*S*,4*S*,5*S*)-4-Azido-5-(triisopropylsilyloxy)-2-oxocyclohexyl (Diethylphosphono)acetate (24). To a solution of phosphonate **10** (1.40 g, 2.76 mmol) in DCM (15 mL) at 0 °C was slowly added a solution of Dess−Martin periodinane[20] (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 $Na_2S_2O_3$ was added, and the mixture was vigorously stirred for 1 h at rt. The usual workup (DCM, H_2O) and purification (50% EtOAc in hexanes) gave **24** (1.16 g, 85%) as a colorless oil: $[\alpha]^{20}_D$ +8.98 (*c* 1.66, $CHCl_3$);[15] IR (film) ν 2948, 2869, 2114, 1743, 1650, 1557, 1456, 1270, 1116, 1027, 966, 882, 683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.56 (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), 1.34 (dt, *J* = 7.1, 1.8 Hz, 6H), 1.22−1.00 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1 (s), 164.5 (d, $J^{13C-31P}$ = 5.8 Hz), 73.2 (d), 68.4 (d), 64.1 (d), 62.7 (td, $J^{13C-31P}$ = 6.3 Hz), 62.5 (td, $J^{13C-31P}$ = 6.3 Hz), 39.7 (t), 35.0 (t), 33.7 (td, $J^{13C-31P}$ = 134.6 Hz), 17.8 (q), 16.2 (qd, $J^{13C-31P}$ = 6.2 Hz), 16.1 (qd, $J^{13C-31P}$ = 6.2 Hz), 11.9 (d); MS (EI) *m*/*z* (rel %) 462 [$M^+ - C_3H_7$] (5), 419 (100), 281 (30), 235 (45), 179 (25), 151 (15), 123 (20); HRMS (EI) calcd for $C_{18}H_{33}N_3O_7PSi$ [$M^+ - C_3H_7$] 462.1825, found 462.1810.

(+)-(5*S*,6*S*,7a*S*)-5-Azido-5,6,7,7a-tetrahydro-6-(triisopropylsilyloxy)benzofuran-2(4*H*)-one (25) and (−)-(6*S*,7a*S*)-7,7a-Dihydro-6-(triisopropylsilyloxy)benzofuran-2(6*H*)-one (26). To a solution of phosphonate **24** (1.99 g, 3.94 mmol) in THF (20 mL) at −78 °C was added over 2 h a solution of potassium *tert*-butoxide (442 mg, 3.94 mmol) in THF (20 mL). The reaction mixture was stirred for 3 h at −78 °C and then was allowed to warm up to rt. Water was added. The usual workup (EtOAc, H_2O) and purification (10% to 20% EtOAc in hexanes) gave **25** (837 mg, 60%) along with **26** (132 mg, 11%) as white solids.

Data for **25**: mp 86−89 °C; $[\alpha]^{20}_D$ +156.8 (*c* 1.35, $CHCl_3$);[15] IR ($CHCl_3$) ν 3023, 2948, 2869, 2109, 1752, 1650, 1540, 1222, 1014, 926, 785 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (s, 1H), 5.07 (dd, *J* = 11.3, 6.5 Hz, 1H), 4.23−4.14 (m, 1H), 4.02−3.94 (m, 1H), 3.05−2.88 (m, 2H), 2.59−2.47 (m, 1H), 1.77−1.65 (m, 1H), 1.19−0.97 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0 (s), 166.9 (s), 116.0 (d), 78.3 (d), 68.9 (d), 61.9 (d), 36.3 (t), 27.9 (t), 18.2 (q), 12.2 (d); MS (EI) *m*/*z* (rel %) 308 [$M^+ - C_3H_7$] (90), 280 (70), 236 (40), 225 (20), 184 (100), 142 (20), 131 (45), 115 (25), 103 (60); HRMS (EI) calcd for $C_{14}H_{22}N_3O_3Si$ [$M^+ - C_3H_7$] 308.1430, found 308.1436.

Data for **26**: mp 73−77 °C; $[\alpha]^{20}_D$ −182.7 (*c* 1.14, $CHCl_3$);[15] IR ($CHCl_3$) ν 3023, 2949, 2870, 2110, 1746, 1645, 1522, 1424, 1215, 1050, 926 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.54 (d, *J* = 9.6 Hz, 1H), 6.28 (dd, *J* = 9.6, 5.1 Hz, 1H), 5.79 (s, 1H), 5.34 (ddd, *J* = 12.5, 4.9, 1.6 Hz, 1H), 4.72−4.63 (m, 1H), 2.64−2.55 (m, 1H), 1.75 (td, *J* = 12.5, 3.6 Hz, 1H), 1.18−0.94 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (s), 163.2 (s), 138.4 (d), 121.0 (d), 112.1 (d), 76.8 (d), 65.2 (d), 38.4 (t), 18.1 (q), 12.3 (d); MS (EI) *m*/*z* (rel %) 308 [M^+] (5), 300 (5), 265 [$M^+ - C_3H_7$] (100), 223 (5), 184 (5), 131 (10), 103 (20); HRMS (EI) calcd for $C_{14}H_{21}O_3Si$ [$M^+ - C_3H_7$] 265.1260, found 265.1266.

(+)-(1*S*,2*R*,8*S*,15*S*)-7-Aza-13-oxa-15-(triisopropylsilyloxy)-tetracyclo[6.5.2.0.^{2,7}0^{1,10}]pentadec-10-en-12-one (28). To a solution of bromide **7** (6.6 mg, 0.014 mmol) in EtOH (1.4 mL) at rt was added palladium on carbon (10 wt.%, 0.15 mg). The reaction mixture was stirred for 2 h at rt under hydrogen atmosphere. The solution was filtered on Celite (EtOAc washings). The solvent was evaporated under reduced pressure and the usual purification (15% EtOAc in hexanes) gave **28** (4.0 mg, 73%) as a colorless oil: $[\alpha]^{20}_D$ +16.9 (*c* 0.40, $CHCl_3$);[15] IR (film) ν 2945, 2866, 1765, 1653, 1462, 1151, 1113, 1061, 1012, 881, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (br. s, 1H), 4.39−4.31 (m, 1H), 3.00 (d, *J* = 18.2 Hz, 1H), 2.94−2.82 (m, 2H), 2.81−2.61 (m, 4H), 1.86−1.75 (m, 1H), 1.62−1.40 (m, 4H), 1.37−1.20 (m, 1H), 1.11−0.96 (m, 21H), 0.92−0.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3 (s), 174.1 (s), 111.5 (d), 84.6 (s), 65.6 (d), 65.3 (d), 59.9 (d), 52.8 (t), 42.4 (t), 29.5 (t),

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26.7 (t), 25.8 (t), 24.1 (t), 18.1 (q), 12.1 (d); MS (EI) *m*/*z* (rel %) 391 [M^+] (25), 348 [$M^+ - C_3H_7$] (85), 218 (30), 191 (100), 163 (10), 110 (10); HRMS (EI) calcd for $C_{22}H_{37}NO_3Si$ [M^+] 391.2543, found 391.2536.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies ^1H and ^{13}C NMR spectra for all new compounds and copy of NOESY spectrum for compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Snieckus, V. iIn *The Alkaloids*; Academic Press: New York, 1973; Vol. *14*, pp 425−506.

(2) Beutler, J. A.; Karbon, E. W.; Brubaker, A. N.; Malik, R.; Curtis, D. R.; Enna, S. J. *Brain Res.* **1985**, *330*, 135−140.

(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.

(4) Arbain, D.; Birkbeck, A. A.; Byrne, L. T.; Sargent, M. V.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1863−1869.

(5) (a) Horii, Z.; Ikeda, M.; Tamura, Y.; Saito, S.; Kotera, K.; Iwamoto, T. *Chem. Pharm. Bull.* **1965**, *13*, 1307−1311. (b) The same initially proposed structures for securinol A and B by Horii (ref 5a) were mistakenly used again by Raj in 2008 (Raj, D.; Łuczkiewicz, M. *Fitoterapia* **2008**, *79*, 419−427), even though the structure had already been corrected by Arbain and Sargent in 1991 (ref 4).

(6) Horii, Z.; Yamauchi, M.; Ikeda, M.; Momose, T. *Chem. Pharm. Bull.* **1970**, *18*, 2009−2012.

(7) For the development of the Vilsmeier−Haack cyclization, see: (a) Bélanger, G.; Larouche-Gauthier, R.; Ménard, F.; Nantel, M.; Barabé, F. *Org. Lett.* **2005**, *7*, 4431−4434. (b) Bélanger, G.; Larouche-Gauthier, R.; Ménard, F.; Nantel, M.; Barabé, F. *J. Org. Chem.* **2006**, *71*, 704−712. For the development of one-pot Vilsmeier−Haack and Mannich cyclizations, see: (c) Bélanger, G.; O'Brien, G.; Larouche-Gauthier, R. *Org. Lett.* **2011**, *13*, 4268−4271.

(8) Larouche-Gauthier, R.; Bélanger, G. *Org. Lett.* **2008**, *10*, 4501−4504.

(9) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.

(10) (a) Katritzky, A. R.; Chang, H.-X.; Yang, B. *Synthesis* **1995**, 503−505. (b) Pasqua, A. E.; Matheson, M.; Sewell, A. L.; Marquez, R. *Org. Process Res. Dev.* **2011**, *15*, 467−470.

(11) The enantiomeric ratio was determined by gas chromatography. See Experimental Section.

(12) Wu, M. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1997**, *38*, 1693−1696.

(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 based on the enantiomeric ratio of compound (+)-**22** from which it is derived.

(16) (a) Anderson, A. G.; Stang, P. J. *Org. Synth.* **1981**, *60*, 34−39. (b) Anderson, A. G.; Stang, P. J. *J. Org. Chem.* **1976**, *41*, 3034−3036.

(17) Deng, B.-L.; Hartman, T. L.; Buckheit, R. W.; Pannecouque, C.; De Clercq, E.; Fanwick, P. E.; Cushman, M. *J. Med. Chem.* **2005**, *48*, 6140−6155.

(18) Leighton, J. L.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 389−390.

(19) Hill, G. J.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3607−3608.

(20) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899−2899.