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Concise Total Syntheses of (±)-Strychnine and (±)-Akuammicine†

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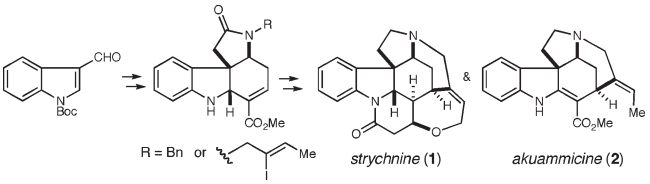

Concise total syntheses of *Strychnos* alkaloids strychnine (**1**) and akuammicine (**2**) have been realized in 13 and 6 operations, respectively. Key steps include (1) the vinylogous Mannich reaction; (2) a novel, sequential one-pot spirocyclization/intramolecular aza-Baylis−Hillman reaction; and (3) a Heck cyclization. The synthesis of **1** proceeds via the Wieland−Gumlich aldehyde (**26**).

The indole alkaloids strychnine (**1**)[1] and akuammicine (**2**)[2] are characteristic members of the *Strychnos* family whose complex structures have fascinated synthetic organic chemists for over half a century (Figure 1).

The total synthesis of strychnine (**1**) by Woodward in 1954 ushered in the era of complex natural product total synthesis.[3] Nearly four decades elapsed before subsequent syntheses were reported by Magnus,[4] Stork,[5] Overman,[6] Kuehne,[7] Rawal,[8] Martin (formal),[9] and Bonjoch-Bosch,[10] which were reviewed in 2000.[11] The turn of the century further chronicled syntheses by Vollhardt,[12] Mori,[13] Bodwell (formal),[14] Shibasaki,[15] Fukuyama,[16] and Padwa,[17] which were also reviewed in 2007.[18] Syntheses of the simpler congener akuammicine (**2**) have been reported by Overman,[19] Kuehne,[20] Bonjoch-Bosch,[21] Martin,[9a] and Rawal.[22] These alkaloids continue to offer excellent opportunities for showcasing novel synthetic methods aimed at efficiently assembling complex, polycyclic targets.

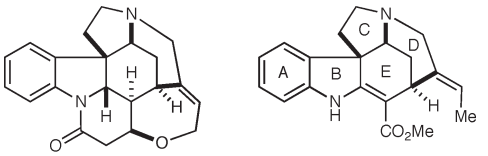

FIGURE 1. Structures of *Strychnos* alkaloids **1** and **2**.

We recently disclosed a novel sequential one-pot spirocyclization/intramolecular aza-Baylis−Hillman (IABH) protocol for efficiently assembling the ABCE tetracyclic framework of *Strychnos* alkaloids **1** and **2**.[23]

Sequential (tandem) one-pot reactions, much like domino (cascade) methods, enable a marked rise in both molecular complexity and synthetic efficiency in a single operation.[24] In this paper, we report a streamlined route to the ABCE tetracyclic cores of strychnine (**1**) and akuammicine (**2**), in addition to concise total syntheses thereof.

The synthesis of **2** began with commercially available *N*-Boc-indole 3-carboxaldehyde (**4**) (Scheme 1).

Condensation of **4** with known allylic amine **5**,[25] which was prepared in one step from the commercially available bromide precursor, afforded imine **6**. Treatment of **6** with vinyl silyl ketene acetal **7** and bromoacetyl chloride (**8**) effected a vinylogous Mannich reaction via the intermediary *N*-acyliminium species **9**.[26] Termination of the reaction with

† Dedicated to Prof. David Dalton on the occasion of his 73rd birthday.

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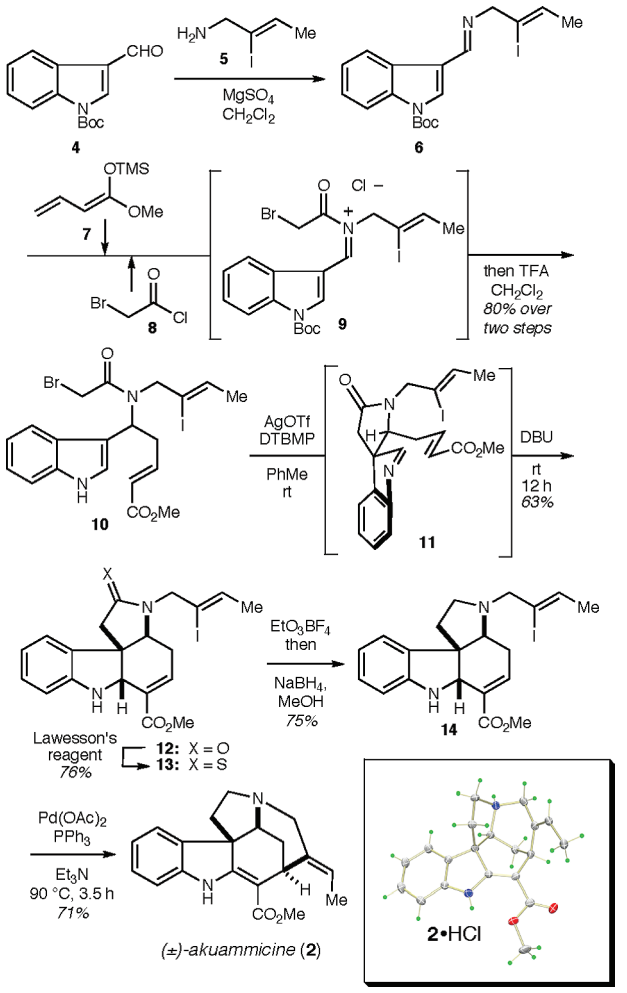
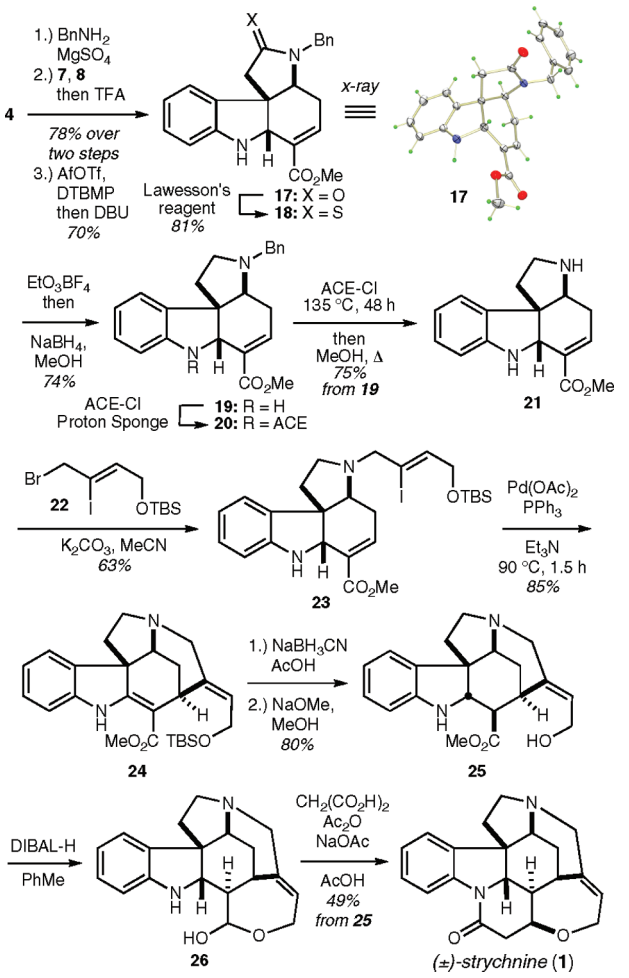
SCHEME 1. Total Synthesis of Akuammicine (2)



SCHEME 2. Total Synthesis of Strychnine (1)



TFA removed the *N*-Boc protecting group, furnishing **10** in 80% yield over two steps. We then subjected **10** to our sequential one-pot spirocyclization/IABH protocol: (1) AgOTf and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) generated spiroindolenine **11** bearing the C-ring and (2) subsequent addition of 3 equiv of DBU triggered an intramolecular aza-Baylis−Hillman reaction, delivering ABCE tetracycle **12** in 63% yield.[23]

At this juncture, readjustment of the C ring oxidation state was in order (see Figure 1). The presence of the vinyl iodide and conjugated ester moieties precluded reduction with $LiAlH_4$ or similar reducing agents. As the classical Borch[27] protocol for amide reduction was ineffective, recourse to the Raucher[28] variant (i.e., thia-Borch) was made. To this end, thionation of **12** with Lawesson's reagent afforded thiolactam **13** in 76% yield. Alkylation of **13** with Meerwein's salt and reduction of the intermediary thioimidate with $NaBH_4$ and methanol furnished tetracycle **14** in a single operation (75% yield).

With **14** in hand, endgame inspired by Rawal's highly efficient, intramolecular Heck reaction was pursued.[8] In the event, heating a solution of **14**, catalytic $Pd(OAc)_2$, and PPh_3 in Et_3N at 90 °C for 3.5 h secured **2** in 71% yield.[10] Treatment of **2** with ethereal HCl and slow evaporation of the salt from CH_2Cl_2 afforded material suitable for single-crystal X-ray analysis, which heretofore had not been reported and unambiguously confirmed the natural product's structure (Scheme 1). Thus, the total synthesis of akuammicine (**2**) was accomplished in six steps (20% overall yield) from commercially available **4**.

In order to maximize synthetic convergence to strychnine (**1**), we employed the *N*-benzyl protecting group and postponed side-chain installation to later in the synthesis (Scheme 2). Condensation of **4** with benzylamine and application of the aforementioned vinylogous Mannich protocol proceeded in 78% yield over two steps. Subjection of this product to the one-pot spirocyclization/IABH protocol delivered tetracycle **17** in 70% yield.[23]

The reduction of lactam **17** via the Raucher procedure afforded **19** in 60% yield over two steps. At this stage, various methods for *N*-debenzylation were screened. Optimal conditions included stepwise treatment of **19** with (1) α-chloroethyl chloroformate (ACE-Cl)[29] and Proton Sponge to protect the indoline nitrogen and (2) heating **20** in neat ACE-Cl at 135 °C for 48 h followed by methanolysis, which furnished **21** in 75% yield from **19**.[10]

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Alkylation of amine **21** with bromide **22**[8] secured Heck precursor **23** in 63% yield. After subjecting **23** to previous Heck conditions (Scheme 1), we obtained pentacycle **24** in 85% yield, which had been prepared by Martin and Rawal.[9b,22] Reduction of the vinylogous carbamate with $NaBH_3CN$ in AcOH followed by base-mediated epimerization of the methyl ester yielded **25**, which had been prepared by Overman,[6] Kuehne,[7b] Bonjoch-Bosch,[10] and Fukuyama.[16] Reduction of ester **25** with DIBAL-H afforded the Wieland−Gumlich aldehyde (**26**), which was converted into **1** using Robinson's protocol in 49% yield over two steps.[30] Thus, the total synthesis of strychnine (**1**) was accomplished in 13 steps (5% overall yield) from commercially available **4**.

In summary, we have reported concise total syntheses of *Strychnos* alkaloids strychnine (**1**) and akuammicine (**2**) by employing the vinylogous Mannich reaction, our novel sequential one-pot spirocyclization/IABH protocol, and the intramolecular Heck reaction as key steps. We are currently streamlining the synthetic routes to these and other *Strychnos* targets, in addition to developing asymmetric variants thereof.

Experimental Section

Akuammicine (2). Palladium(II) acetate (7.0 mg, 0.0313 mmol) and PPh_3 (16.4 mg, 0.0626 mmol) were added to a solution of **14** (47 mg, 0.1044 mmol) in Et_3N (5 mL). The reaction mixture was purged with argon for 10 min, heated to 90 °C (oil bath), and stirred for 3.5 h. After being cooled to rt, the mixture was diluted with CH_2Cl_2 (25 mL), washed with brine (10 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with $MeOH/CH_2Cl_2$ (0.4:9.6→1:9). Purified **2** was washed with a solution of 25% aq NaOH (10 mL), which afforded 24 mg (71%) of **2** as white solid whose NMR spectra (^1H and ^{13}C) were identical with reported literature values (see refs 9a and 19−22).

Thiolactam 18. Lawesson's reagent (1.70 g, 4.21 mmol) was added to a stirred solution of **17** (2.63 g, 7.02 mmol) in toluene (70 mL) and stirred for 1 h at 100 °C, after which TLC showed full consumption of starting material. The reaction mixture was cooled to rt, concentrated to ∼10 mL, and purified by flash column chromatography eluting with EtOAc/hexanes (1:3) to afford 2.22 g (81%) of **18** as a pale yellow oil: IR (neat) 3386, 1708, 1606, 1484, 1466, 1437, 1264, 907 cm^{-1}; ^1H NMR (400 MHz) δ 7.30−7.24 (m, 5H), 7.02 (td, J = 7.5, 1.2 Hz, 1H), 6.95 (d, J = 7.2 Hz, 1H), 6.84 (t, J = 4.4 Hz, 1H), 6.65 (t, J = 7.4 Hz, 1H), 6.54 (d, J = 7.6 Hz, 1H), 5.36 (d, J = 14.6 Hz, 1H), 4.62 (d, J = 14.6 Hz, 1H), 4.42 (s, 1H), 3.85 (t, J = 5.8 Hz, 1H), 3.76 (s, 3H), 3.32 (d, J = 17.6 Hz, 1H), 3.21 (d, J = 17.6 Hz, 1H), 2.47 (dt, J = 19.2, 5.4 Hz, 1H), 2.30 (dt, J = 19.2, 4.7 Hz, 1H); ^{13}C NMR (100 MHz) 200.3, 166.2, 149.1, 136.2, 134.5, 130.8, 130.6, 129.0, 128.7, 128.4, 128.2, 128.1, 122.6, 119.2, 109.5, 65.3, 59.4, 56.2, 52.0, 50.0, 49.7, 27.1; HRMS (FAB) calcd for $C_{23}H_{22}N_2O_2S + H^+$ = 391.1480, found 391.1466.

Tetracycle 19. Triethyloxonium tetrafluoroborate (5.56 mL, 1 M in CH_2Cl_2, 5.56 mmol) was added to a solution of **18** (1.97 g, 5.07 mmol) in 50 mL of CH_2Cl_2 at 0 °C and stirred for 20 min. The reaction mixture was warmed to rt and stirred for 45 min. The reaction mixture was recooled to 0 °C, and additional triethyloxonium tetrafluoroborate (5.56 mL, 1 M in CH_2Cl_2, 5.56 mmol) was added. The reaction mixture was stirred for 15 min, warmed to rt, and stirred for an additional 30 min. The solvent was evaporated under reduced pressure, and the residue was dissolved in 50 mL of dry MeOH. After the mixture was cooled to 0 °C, excess $NaBH_4$ (1.15 g, 30.27 mmol) was added, and the reaction was stirred for 10 min. After being warmed to rt, the mixture was stirred for an additional 2.0 h. The solvent was evaporated under reduced pressure; the mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 × 60 mL). The combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with EtOAc/hexanes (1:9) to afford 1.35 g (74%) of **19** as a colorless foam: IR (neat) 3409, 3029, 2950, 2800, 1704, 1656, 1464, 1453, 1399, 1264, 1099 cm^{-1}; ^1H NMR (500 MHz) δ 7.27−7.19 (m, 5H), 7.05 (dd, J = 7.3, 0.8 Hz, 1H), 7.01−6.98 (m, 2H), 6.69 (td, J = 7.5, 1.2 Hz, 1H), 6.54 (d, J = 8.0 Hz, 1H), 4.52 (bs, 1H), 4.31 (s, 1H), 3.93 (d, J = 13.3 Hz, 1H), 3.76 (s, 3H), 3.45 (d, J = 13.3 Hz, 1H), 3.04 (t, J = 3.5, Hz, 1H), 3.02−2.97 (m, 1H), 2.61−2.56 (m, 1H), 2.43−2.38 (m, 1H), 2.28−2.23 (m, 1H), 2.14−2.08 (m, 1H), 1.94−1.88 (m, 1H); ^{13}C NMR (125 MHz) 167.4, 150.1, 139.4, 139.2, 132.9, 130.1, 128.4, 128.2, 128.0, 126.8, 122.9, 118.5, 109.0, 63.6, 61.4, 57.6, 53.5, 51.7, 50.9, 37.8, 25.1; HRMS (FAB) calcd for $C_{23}H_{24}N_2O_2 + H^+$ = 361.1916, found 361.1908.

Amine 21. ACE-Cl (625 mg, 4.37 mmol) and Proton Sponge (375 mg, 1.75 mmol) were added to a solution of **19** (315 mg, 0.85 mmol) in DCE (8 mL) at 0 °C. The reaction mixture was heated to 90 °C and stirred for 16 h at that temperature. The reaction mixture was cooled to rt and diluted with CH_2Cl_2 (50 mL). The organic layers were washed with 1 N aq HCl (15 mL), satd aq $NaHCO_3$ (20 mL), and brine (20 mL). The organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in ACE-Cl (1.5 mL), and the reaction mixture was heated to 135 °C (bath temperature) and stirred for 48 h at that temperature. The reaction mixture was cooled to rt and concentrated. The crude product was dissolved in MeOH (10 mL) and heated to 70 °C (bath temp) for 3 h. The reaction mixture was cooled and concentrated, and the residue was purified by flash column chromatography eluting with $CH_2Cl_2/MeOH/NH_4OH$ (8.9:1:0.1) to afford 173 mg (75%) of **21** as a foam: IR (neat) 3409, 3053, 2952,1706, 1607, 1484, 1264, 906 cm^{-1}; ^1H NMR (400 MHz) δ 7.08−7.01 (m, 3H), 6.72 (td, J = 7.6, 0.9 Hz, 1H), 6.59 (d, J = 7.6 Hz, 1H), 4.63 (bs, 1H), 4.37 (s, 1H), 4.08 (bs, 1H), 3.78 (s, 3H), 3.62 (t, J = 4.4 Hz, 1H), 3.38−3.23 (m, 2H), 2.50 (t, J = 4.4 Hz, 1H), 2.31−2.24 (m, 1H), 2.14−2.07 (m, 1H); ^{13}C NMR (100 MHz) δ 167.0, 150.0, 138.2, 131.0, 130.3, 128.5, 122.3, 118.7, 109.3, 59.9, 58.3, 53.4, 51.9, 43.5, 39.2, 26.9; HRMS (FAB) calcd for $C_{160}H_{18}N_2O_2 + H^+$ = 271.1447, found 271.1443.

Vinyl Iodide 23. Allyl bromide **22** (121 mg, 0.31 mmol) and K_2CO_3 (58 mg, 0.42 mmol) were added to a solution of **21** (76 mg, 0.28 mmol) in MeCN (3 mL) at 0 °C. The reaction mixture was stirred for 16 h at 0 °C, quenched with water (5 mL), extracted with CH_2Cl_2 (2 × 20 mL), and washed with brine (10 mL). The solvent was dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with EtOAc/hexanes (1.2:8.8) to afford 102 mg (63%) of **23** as colorless oil: IR (neat) 3053, 2985, 1706, 1422, 1264, 906 cm^{-1}; ^1H NMR (400 MHz) δ 7.10 (dd, J = 7.2, 0.8 Hz, 1H), 7.05−7.01 (m, 2H), 6.70 (td, J = 7.4, 0.7 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.08 (t, J = 5.2 Hz, 1H), 4.58 (bs, 1H), 4.31 (s, 1H), 4.26 (d, J = 5.2 Hz, 2H), 3.78 (s, 3H), 3.57 (dd, J = 14.8, 1.6, Hz, 1H), 3.29 (d, J = 14.8 Hz, 1H), 3.17(t, J = 3.8 Hz, 1H), 3.14−3.09 (m, 1H), 2.69 (td, J = 9.6, 4.4 Hz, 1H), 2.37 (dt, J = 14.8, 3.6 Hz, 1H), 2.29−2.22 (m, 1H), 2.20−2.14 (m, 1H), 2.01−1.95 (m, 1H), 0.91 (s, 9H), 0.89 (s, 6H); ^{13}C NMR (100 MHz) 167.3, 150.0, 139.1, 135.9, 132.4, 130.0, 128.1, 123.1, 118.4, 109.0, 105.4, 68.0, 65.1, 62.4, 61.1, 53.4, 51.7, 50.4, 37.6, 25.9, 25.2, 18.2, −5.2; HRMS (FAB) calcd for $C_{26}H_{37}N_2O_3SiI + H^+$ = 581.1696, found 581.1694.

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Pentacycle 24. Palladium(II) acetate (10.4 mg, 0.0465 mmol) and PPh_3 (24.4 mg, 0.0930 mmol) were added to a solution of **23** (90 mg, 0.155 mmol) in Et_3N (7.3 mL). The reaction mixture was purged with argon for 10 min, heated to 90 °C (bath temperature), and stirred for 2 h. After being cooled to rt, the mixture was diluted with EtOAc (25 mL). The combined organic layers were washed with 25% aq NaOH (10 mL) and brine (10 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with MeOH/CH_2Cl_2 (0.2:9.8 → 1:9) to afford 60 mg (85%) of **24** as a colorless oil whose NMR spectra (^1H and ^{13}C) were identical with reported literature values (see ref 9b).

Ester 25. To a solution of **24** (60 mg, 0.133 mmol) in glacial AcOH (1.4 mL) at 10 °C was added $NaCNBH_3$ (42 mg, 0.663 mmol). The reaction mixture was stirred for 1 h, cooled to 0 °C, and basified with 30% NH_4OH solution to pH 10. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), washed with brine (10 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure and dried under vacuum for 1 h. The crude residue was dissolved in MeOH/THF (1:1, 4.8 mL) and treated dropwise with NaOMe (90 μL, 25% in MeOH, 0.399 mmol). After being stirred for 5 h, the reaction mixture was cooled to 0 °C, quenched with 2 N aq HCl (5 mL) solution, and stirred for an additional 3 h. The pH was adjusted to 10 by the addition of 30% NH_4OH. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), washed with brine (10 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure, and the crude product was purified by flash column chromatography eluting with CH_2Cl_2/MeOH/NH_4OH (8.4:1.5:0.1) to afford 36 mg (80%) of **25** as a white powder whose NMR spectra (^1H and ^{13}C) were identical with reported literature values (see refs 6 and 10).

Strychnine (1). To a solution of **25** (36 mg, 0.106 mmol) in CH_2Cl_2 (2 mL) cooled to −78 °C was slowly added DIBAL-H (0.32 mL, 1 M in cyclohexane, 0.32 mmol). After 45 min, additional DIBAL-H (0.15 mL, 1 M in cyclohexane, 0.15 mmol) was added, and the reaction mixture was stirred for an additional 15 min. The reaction was quenched with MeOH (1 mL) followed by 30% Rochelle's salt (5 mL) and then warmed to rt. The reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL), washed with brine (10 mL), dried (Na_2SO_4), and filtered. The solvent was concentrated under reduced pressure to afford crude Wieland−Gumlich aldehyde (**26**). To **26** were added glacial AcOH (1.4 mL), NaOAc (174 mg, 2.12 mmol), malonic acid (183 mg, 1.68 mmol), and Ac_2O (36 mg, 0.353 mmol). The reaction mixture was heated to 110 °C (bath temperature) and stirred for 2 h, after which it was cooled to rt, diluted with water (12 mL), washed with 50% aq NaOH (10 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with $CHCl_3$/MeOH (8.8:1.2) to afford 17 mg (49%) of strychnine (**1**) as a white powder whose NMR spectra (^1H and ^{13}C) were identical with natural **1** purchased from the Aldrich Chemical Company.

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Supporting Information Available: General and experimental procedures for **10** and **12**−**14** and NMR spectra (^1H and ^{13}C) for **1** (synthetic and natural), **2**, **10**, **12**−**14**, **18**, **19**, **21**, and **23**−**25**. Crystallographic details of **2**-HCl (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.