Syntheses of Strychnos- and Aspidospermatan-Type Alkaloids. 6. Total Syntheses of (±)-Echitamidine, (±)-Alstogustine, (±)-19-*epi*-Alstogustine, and (±)-Akuammicine

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19-Oxodihydroakuammicine was obtained in a three-pot sequence, in 25% overall yield based on a new condensation–sigmatropic rearrangement sequence. Reductions and quaternization reactions furnished the title compounds.

In the preceding paper of this series,[1] we reported syntheses of (±)-echitamidine (**1** in Scheme 2) and its C-20 and C-19,20 epimers (**2**, **3** in Scheme 2), based on the intramolecular Diels–Alder reactions of indoloacrylate and enamine functionalities that had been incorporated into an indoloazonine skeleton.[2] As an alternative to that synthetic methodology, we have now also applied a condensation–sigmatropic rearrangement sequence (Scheme 1),[3] which we had previously used in the synthesis of strychnine,[4] to this project.

The present report allows a direct comparison of the two synthetic strategies, since both converge at (±)-19-oxo-20-*epi*-19,20-dihydroakuammicine (**4**), the penultimate intermediate in the synthesis of echitamidine (**1**). Furthermore, syntheses of the derived quaternary salts (±)-alstogustine (**5**) and (±)-19-*epi*-alstogustine (**6**, in Scheme 2) and of (±)-akuammicine (**7**, in Scheme 3) could now be obtained.

For the present syntheses, the formylacetone ketal (**8**) was extended to its vinylogue **9** by a Wittig reaction (86%). On heating of this unsaturated aldehyde with *N*-benzyl-2-((methoxycarbonyl)methyl)tryptamine (**10**) and BF_3 etherate, the tetracyclic ketal **11** was obtained (30%) as a single diastereomer. Debenzylation, by hydrogenolysis with ammonium formate and Pd/C, then provided the secondary amine **12**.

For closure of ring D of the strychnos alkaloid skeleton, the unpurified amine **12** was condensed with formaldehyde. On addition of HCl, the resulting imonium–ketal intermediate **13** underwent cyclization.[5] Hydrolysis of the ketal function then produced the ketone **4** in 83% overall yield from the tetracyclic ketal **11**. NOESY spectra of ketone **4** are consistent with the assigned stereochemistry (Figure 1). Thus, the pentacyclic strychnos alkaloid skeleton, with all required functionality, was obtained in a three-pot operation from the aldehyde **9** and the tryptamine derivative **10** in 25% overall yield.

Epimerization (1:2) of the ketone **4** at C-20 with sodium methoxide (Scheme 2) provided the ketone **14**. The ketones **4** and **14** did not epimerize with HCl in methanol.

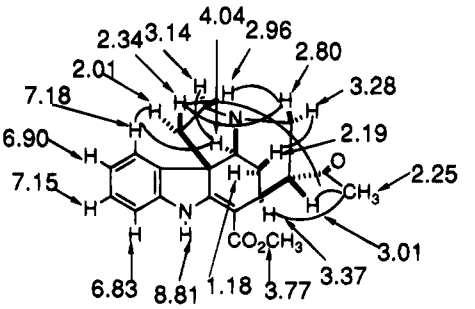

Figure 1. NOE of ketone **4**.

Consequently, the epimer **4** must have been generated stereoselectively in the intramolecular Mannich-like cyclization reaction.

Stereoselective reduction of the ketone **14** with sodium borohydride provided echitamidine (**1**).[1] Reduction of the ketone **4** to the two epimeric alcohols **2** and **3** (24%:68%) with sodium borohydride, or selectively to the latter with $NaBH_4$ and $CeCl_3$, thus gave (±)-*epi*-echitamidine ((±)-demethylalstogustine (**3**), 92%). Quaternization of the alcohols **2** and **3** with methyl iodide then furnished (±)-19-*epi*-alstogustine (**5**) and (±)-alstogustine (**6**), respectively.[6]

Attempted dehydrations of echitamidine (**1**) or of its epimers **2** and **3** with Burgess reagent or triphenylphosphine/CCl_4, for the generation of akuammicine (**7**), were not encouraging. Consequently (Scheme 3), the ketone **4** was converted to a thio enol ether (**15**) (63%). Only the *E* isomer of this compound was formed with benzyl mercaptan and BF_3, together with some 20-acetoxy thioether **16** (12%). Repulsion of charges in a BF_3-complexed aminoacrylate thionium intermediate could be expected to lend selectivity to formation of the desired double bond stereochemistry. *E* double bond geometry of the thio enol ether **15** was demonstrated by NOESY spectra (Figure 2). The acetoxy thioether **16** could be hydrolyzed back to the ketone **4**.

Akuammicine (**7**)[7] was formed on hydrogenolysis of the thioenol ether **15** with Raney nickel (83%).

Experimental Section

4-(2-(2-Methyl-1,3-dioxalanyl))but-2-enal (9). A solution of 2-(2-(2-methyl-1,3-dioxalanyl))ethanal[8] (6.60 g, 50.7 mmol) and (formylmethylene)triphenylphosphorane (18.5 g, 60.9

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(1) Kuehne, M. E.; Brook, C. S.; Frasier, D. A.; Xu, F. *J. Org. Chem.* **1994**, *59*, 5977.

(2) The biogenetic numbering system used for all compounds is that of Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508. Lettering of the fused ring systems follows the same implied principle.

(3) Parsons, R. P.; Berk, J. D.; Kuehne, M. E. *J. Org. Chem.* **1993**, *58*, 7482.

(4) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490.

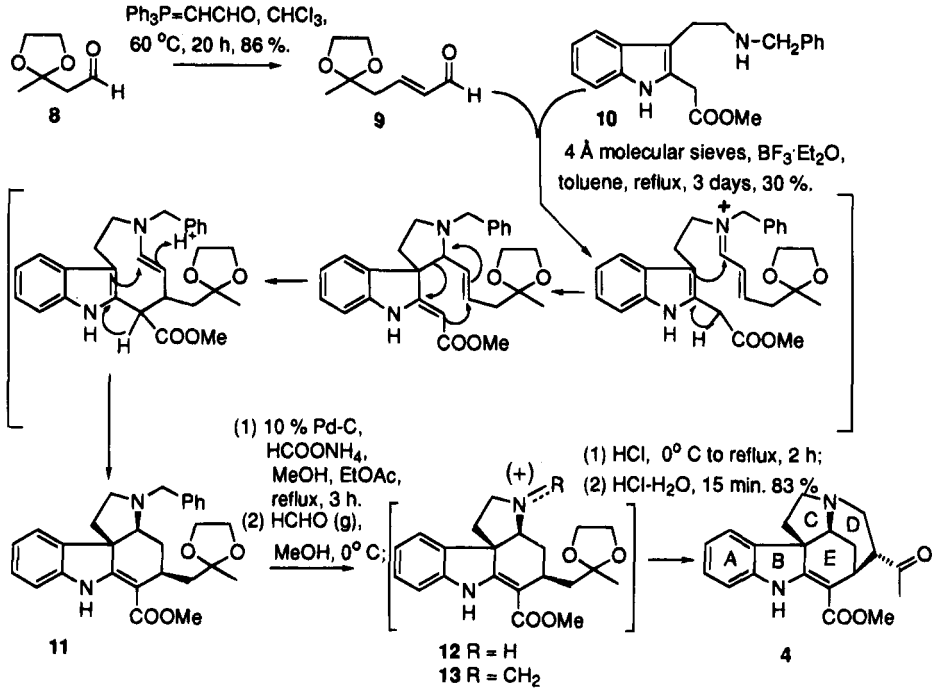
(5) Intramolecular alkylation of ketals by imonium intermediates was first described by Wenkert (Wenkert, E. *Acc. Chem. Res.* **1968**, *1*, 78) and used for the synthesis of iboxyphylline (Kuehne, M. E.; Pitner, J. B. *J. Org. Chem.* **1989**, *54*, 4553 and other compounds referenced there).

(6) (a) Hu, W.-L.; Zhu, J.-P.; Prewo, R.; Hesse, M. *Phytochem.* **1989**, *28*, 1963. (b) Massiot, G.; Boumendjel, A.; Nuzillard, J.-M.; Richard, B.; Le Men-Olivier, L.; David, B.; Hadi, H. A. *Phytochem.* **1992**, *31*, 1078.

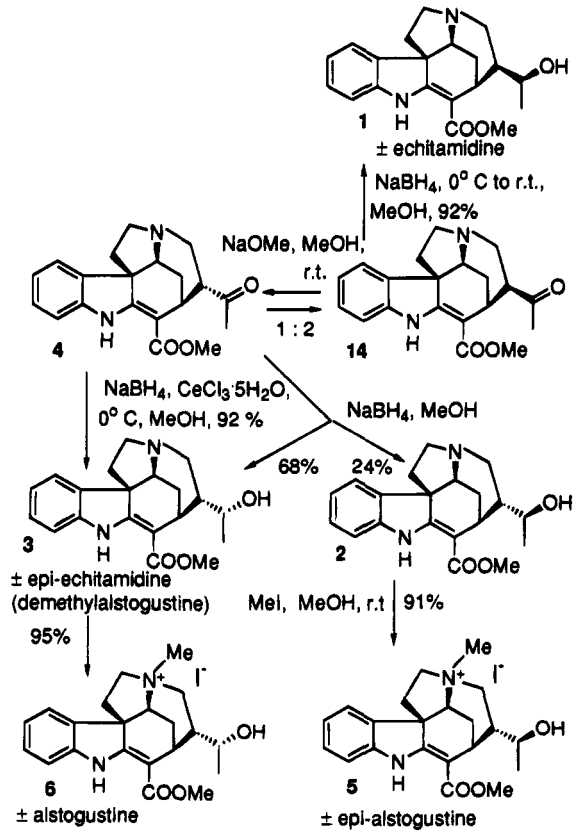
(7) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966.

0022-3263/94/1959-7803$04.50/0

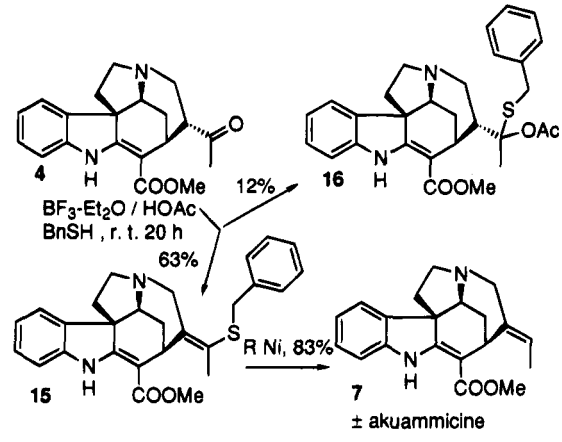
Scheme 1



Scheme 2



Scheme 3



mmol) in 100 mL of chloroform was heated at 60 °C for 20 h. Concentration and chromatography (EtOAc/Hex, 1:4) gave 6.8 g (86%) of the title aldehyde as an oil.

When benzene was used instead of chloroform, the yield was only 37%. **9**: TLC R_f = 0.24 (EtOAc/Hex, 1:4); IR (film) ν_{max} 2978, 2881, 1683, 1646, 1537, 1504, 1211, 1150, 1121, 1039, 663 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.53 (d, J = 8 Hz, 1 H), 6.84 (dt, J = 7, 16 Hz, 1 H), 6.18 (dd, J = 8, 16 Hz, 1 H), 3.99 (m, 4 H), 2.68 (d, J = 7 Hz, 2 H), 1.36 (s, 3 H); MS m/z (rel intensity) 156 (M^+, 2), 131 (4), 99 (9), 87 (100).

Methyl 5-(2-(2-Methyl-1,3-dioxalanyl))-3-(phenylmethyl)-2,3,3a,4,5,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (11). To a solution of methyl 3-[2-(N^b-{phenylmethyl}amino)ethyl]indole-2-ethanoate (**10**, 377 mg, 1.16 mmol)[8] in 8 mL of dry toluene was added freshly activated 4-Å molecular sieves powder (400 mg), followed by aldehyde **9** (200 mg, 1.28 mmol). The flask was equipped with a Dean–Stark separator, which was filled with freshly activated 4-Å molecular sieves. The system was degassed with Ar, and BF_3·Et_2O (4 μL, 0.035 mmol) was added. The reaction mixture was heated at vigorous reflux for 3 days and then cooled to room temperature. The solid was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was purified on a silica gel column, eluting with CH_2Cl_2/EtOAc/Hex (5:15:80), to give 160 mg (30% yield) of product as a white foam. **11**: TLC R_f = 0.28 (EtOAc/Hex, 1:4; CAS violet, faded fast to orange); UV (EtOH) λ_{max} 324, 298, 210 nm; IR (KBr) ν_{max} 3359, 2971, 2936, 2781, 1675, 1609, 1462, 1270, 1230, 1208, 1186, 1145, 1101, 1041, 738, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (s, 1 H), 7.42 (d, J = 7.5 Hz, 2 H), 7.33 (t, J = 7.3 Hz, 2H), 7.25 (t, J = 7.3 Hz, 1 H), 7.12 (t, J = 7.7 Hz, 1 H), 7.01 (d, J = 7.3 Hz, 1 H), 6.82 (t, J = 7.5 Hz, 1 H), 6.79 (d, J = 7.8 Hz, 1 H), 4.25 (d, J = 13.2 Hz, 1 H), 3.98 (s, 4 H), 3.78 (s, 3 H), 3.56 (d, J = 13.2 Hz, 1 H), 3.33 (d, J = 5.5 Hz,

(8) Kelly, T. R.; Ananthasubramanian, L.; Borah, K.; Gillard, J. W.; Goerner, R. N.; King, P. F.; Lyding, J. M.; Tsang, W.-G.; Vaja, J. *Tetrahedron* **1984**, *40*, 4569.

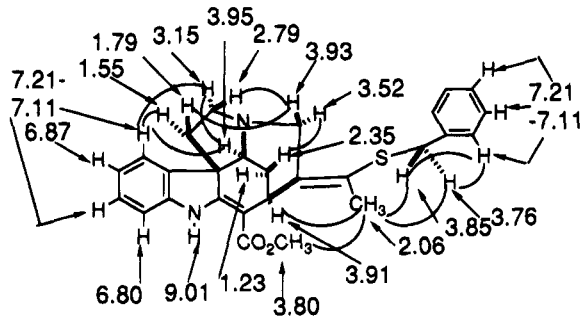


Figure 2. NOE of thio enol ether **15**.

1 H), 3.20 (m, 1 H), 2.93 (m, 2 H), 2.56 (m, 1 H), 2.36 (d, J = 14.0 Hz, 1 H), 2.10 (m, 1 H), 1.80 (d, J = 13.8 Hz, 1 H), 1.69 (dd, J = 4.7, 11.8 Hz, 1 H), 1.47 (s 3 H), 1.31 (m, 1 H); MS *m/z* (rel intensity) 460 (M^+, 16), 327 (9), 225 (12), 194 (3), 180 (7), 167 (4), 146 (30), 134 (4), 91 (33); high-resolution MS, EI ionization, calcd for $C_{28}H_{32}N_2O_4$ 460.2362, found 460.2367.

Methyl 5-(2-(2-Methyl-1,3-dioxalanyl))-2,3,3a,4,5,7-hexahydro-1*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (12). A mixture of ketal **11** (20 mg, 0.043 mmol), $HCOONH_4$ (14 mg, 0.22 mmol), and 10% Pd–C (5 mg, 0.0045 mmol) in 1 mL of MeOH was heated at reflux for 3 h and then cooled to room temperature. Filtration and concentration gave the crude product, which was pure enough for the next reaction step. Purification of the crude product on a silica gel column (CH_2Cl_2/MeOH, 95:5) provided 14 mg (85% yield) of the pure product as a white foam. **12**: TLC R_f = 0.30 (CH_2Cl_2/MeOH, 95:5; CAS brown); UV (EtOH) λ_{max} 326, 298, 210 nm; IR (KBr) ν_{max} 3351, 2945, 2912, 2837, 1673, 1604, 1461, 1435, 1282, 1234, 1197, 1099, 1041, 745 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.18 (s, 1 H), 7.30 (m, 1 H), 7.17 (m, 1 H), 6.90 (m, 2 H), 4.05 (m, 4 H), 3.78 (s, 3 H), 3.23 (m, 3 H), 2.58 (m, 2 H), 2.23 (m, 1 H), 1.93 (m, 3 H), 1.91 (m, 1 H), 1.51 (m, 1 H), 1.41 (s, 3 H).

20-*epi*-19-Oxodihydroakuammicine (4). A mixture of ketal **11** (600 mg, 1.30 mmol), $HCOONH_4$ (411 mg, 6.5 mmol), and 10% Pd–C (138 mg, 0.130 mmol) in 10 mL of MeOH and 5 mL of EtOAc was heated at 60 °C for 1 h and then cooled to room temperature. The solid was removed by filtration and washed with methanol and dichloromethane. The filtrate was concentrated under reduced pressure and was then taken into dichloromethane. The organic phase was washed with saturated $NaHCO_3$. Drying and concentration gave the crude amine **12**.

Into a solution of this secondary amine in 20 mL of MeOH, at 0 °C, was bubbled, via a short glass tube, HCHO gas, which was generated by heating 780 mg of paraformaldehyde (260 mmol) in a 150 °C oil bath under a stream of Ar. Then, 1.5 mL of ether, saturated with HCl (g), was added. The reaction solution was heated at reflux for 2 h, and then 2.5 mL of a 2 N HCl aqueous solution was added. The solution was then heated at reflux for an additional 15 min. The solution was cooled to room temperature, basified with 5% Na_2CO_3 to pH = 8, and extracted with dichloromethane. The residue, obtained on concentration, was purified on a silica gel column, eluting with EtOAc/MeOH/Et_3N (95:5:1), to give 420 mg (83% overall yield for four steps) of the ketone **4** as a white foam: TLC R_f = 0.33 (CH_2Cl_2/MeOH, 95:5, CAS blue); UV (EtOH) λ_{max} 328, 298, 210 nm; IR (KBr) ν_{max} 3355, 2937, 2853, 1698, 1674, 1602, 1471, 1460, 1435, 1280, 1232, 1194, 1162, 1100, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.81 (s, 1 H), 7.18 (d, J = 7.3 Hz, 1 H), 7.15 (t, J = 7.6 Hz, 1 H), 6.90 (t, J = 7.4 Hz, 1 H), 6.83 (d, J = 7.8 Hz, 1 H), 4.04 (s, 1 H), 3.77 (s, 3 H), 3.37 (s, br, 1 H), 3.28 (dd, J = 10.1, 13.9 Hz, 1 H), 3.14 (m, 1 H), 3.01 (ddd, J = 2.6, 5.9, 13.9 Hz, 1 H), 2.96 (m, 1 H), 2.80 (dd, J = 5.9, 13.9 Hz, 1 H), 2.34 (m, 1 H), 2.25 (s, 3 H), 2.19 (ddd, J = 3.3, 3.3, 13.7 Hz, 1 H), 2.01 (m, 1 H), 1.18 (ddd, J = 2.5, 2.5, 13.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.81, 168.64, 167.86, 144.15, 134.99, 127.86, 121.11, 120.66, 109.72, 102.59, 58.55, 58.24, 53.00, 51.07, 49.47, 47.00, 45.15, 29.25, 27.41, 26.58; MS *m/z* (rel intensity) 339 (9), 338 (M^+, 29), 295 (7), 238 (11), 224 (24), 214 (19), 208 (15), 194 (20), 180 (48), 166 (32), 154 (13), 139 (10), 113 (84); high-resolution MS, EI ionization, calcd for $C_{20}H_{22}N_2O_3$ 338.1630, found 338.1632. The product matched the ketone reported in the preceding paper in this series in all analytical data.[1]

(±)-19-*epi*-20-*epi*-Echitamidine (3) and Its 19-Epimer 2. (a) To a solution of the ketone **4** (80 mg, 0.24 mmol) in 2 mL of MeOH at 0 °C was added $NaBH_4$ (18 mg, 0.48 mmol) in several portions. The solution was allowed to stir at room temperature for 1 h. Saturated sodium bicarbonate solution was added to quench the reaction, and the product was extracted with dichloromethane. The residue obtained on concentration was chromatographed on a silica gel column, eluting with CH_2Cl_2/MeOH/Et_3N (90:10:1), to afford 56 mg of 19-*epi*-20-*epi*-echitamidine (**3**, 68% yield) and 20 mg of the 19-epimer (**2**, 24% yield).

(b) To a solution of the ketone **4** (12 mg, 0.036 mmol) in 1 mL of MeOH, at room temperature, was added $CeCl_3 \cdot 5H_2O$ (14 mg, 0.037 mmol). The solution was stirred for 10 min and then cooled to 0 °C. $NaBH_4$ (3.5 mg, 0.093 mmol) was added in several portions, and the solution was stirred at 0 °C for 1 h. Half-saturated sodium bicarbonate solution was added to quench the reaction, and the product was extracted with EtOAc. TLC showed only a trace of the isomer **2**. Purification on a silica gel column gave 11 mg of 19-*epi*-20-*epi*-echitamidine (**3**, 92% yield).

For 19-*epi*-20-*epi*-echitamidine (**3**): mp 168–9 °C (recrystallized from MeOH/EtOAc/Hex); TLC R_f = 0.49 (CH_2Cl_2/MeOH, 9:1; SiO_2 plate deactivated with Et_3N, CAS blue); UV (EtOH) λ_{max} 330, 298, 208 nm; IR (KBr) ν_{max} 3372, 2948, 2870, 1669, 1602, 1473, 1460, 1432, 1381, 1280, 1235, 1196, 1163, 1100, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1 H), 7.21 (d, J = 7.3 Hz, 1 H), 7.15 (t, J = 7.5 Hz, 1 H), 6.91 (t, J = 7.5 Hz, 1 H), 6.84 (d, J = 7.7 Hz, 1 H), 4.05 (s, 1 H), 3.84 (s, 3 H), 3.58 (dq, J = 6.2, 8.1 Hz, 1 H), 3.22 (m, 1 H), 3.01 (m, 1 H), 2.96 (s, 1 H), 2.91 (dd, J = 12.3, 14.2 Hz, 1 H), 2.64 (dd, J = 6.1, 14.2 Hz, 1 H), 2.27 (m, 2 H), 1.98 (m, 1 H), 1.80 (m, 1 H), 1.19 (ddd, J = 2.6, 2.6, 11.0 Hz, 1 H), 1.13 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.80, 167.52, 143.75, 135.53, 127.87, 121.14, 120.81, 109.60, 102.84, 71.01, 58.98, 58.53, 53.74, 51.35, 48.25, 46.49, 45.37, 29.19, 27.24, 20.17; MS *m/z* (rel intensity) 341 (10), 340 (M^+, 64), 322 (9), 309 (4), 295 (7), 281 (6), 263 (7), 252 (6), 240 (10), 225 (100), 214 (20), 208 (19), 193 (27), 180 (67), 167 (37), 154 (11), 139 (48), 115 (32), 100 (14). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.53; H, 7.15; N, 8.08.

For the 19-epimer 2: TLC R_f = 0.3 (CH_2Cl_2/MeOH, 9:1; SiO_2 plate deactivated with Et_3N, CAS blue); UV (EtOH) λ_{max} 328, 300, 208 nm; IR (KBr) ν_{max} 3366, 2943, 2920, 2848, 1667, 1599, 1472, 1461, 1432, 1374, 1282, 1237, 1194, 1160, 1100, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1 H), 7.21 (d, J = 7.2 Hz, 1 H), 7.15 (t, J = 7.6 Hz, 1 H), 6.91 (t, J = 7.5 Hz, 1 H), 6.83 (d, J = 7.7 Hz, 1 H), 4.09 (s, 1 H), 3.83 (m, 1 H), 3.80 (s, 3 H), 3.23 (ddd, J = 6.8, 9.2, 11.6 Hz, 1 H), 3.14 (dd, J = 10.7, 14.0 Hz, 1 H), 3.01 (ddd, J = 4.4, 6.9, 11.6 Hz, 1 H), 2.96 (s, br, 1 H), 2.73 (dd, J = 5.8, 14.0 Hz, 1 H), 2.41 (ddd, J = 6.9, 9.2, 12.9 Hz, 1 H), 2.25 (ddd, J = 3.4, 3.4, 13.5 Hz, 1 H), 2.16 (s, br, OH, 1 H), 2.01 (m, 2 H), 1.27 (d, J = 6.4 Hz, 3 H), 1.21 (ddd, J = 2.6, 2.6, 13.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.88, 144.04, 135.19, 127.95, 121.16, 120.72, 109.69, 103.45, 69.76, 59.31, 57.97, 53.42, 51.72, 47.13, 45.42, 43.14, 29.70, 27.71, 27.25, 20.23; MS *m/z* (rel intensity) 340 (M^+, 5), 294 (3), 225 (18), 208 (6), 194 (11), 179 (16), 166 (11), 156 (8), 154 (10), 151 (17), 139 (40), 114 (21), 94 (100); high-resolution MS, EI ionization, calcd for $C_{20}H_{24}N_2O_3$ 340.1787, found 340.1777.

(±)-Alstogustine (6). A solution of (±)-19-*epi*-20-*epi*-echitamidine[1,9] (**3**, 20 mg, 0.059 mmol) and iodomethane (4.4 μL, 0.071 mmol) in 1 mL of MeOH was stirred at room temperature for 1 h. Concentration, trituration with dichloromethane, and recyrstallization from CH_2Cl_2/MeOH gave 27 mg (95% yield) of (±)-alstogustine (**6**) as white crystals: mp 247 °C; UV (EtOH) λ_{max} 328, 292, 222 nm; IR (KBr) ν_{max} 3370, 2960, 1681, 1601, 1461, 1435, 1245, 1229, 1202, 1115, 1099,

(9) Boonchuay, W.; Court, W. E. *Phytochemistry* **1976**, *15*, 821.

1017, 750 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.53 (d, J = 7.4 Hz, 1 H), 7.26 (t, J = 7.7 Hz, 1 H), 7.02 (d, J = 7.8 Hz, 1 H), 6.98 (t, J = 7.5 Hz, 1 H), 4.53 (s, 1 H), 3.94 (m, 1 H), 3.82 (s, 3 H), 3.80 (m, 1 H), 3.77 (dq, J = 3.0, 6.5 Hz, 1 H), 3.64 (dd, J = 6.2, 13.4 Hz, 1 H), 3.51 (s, 3 H), 3.45 (dd, J = 13.1, 13.1 Hz, 1 H), 3.38 (s, br, 1 H), 2.66 (ddd, J = 6.9, 9.7, 14.3 Hz, 1 H), 2.46 (ddd, J = 3.2, 3.2, 15.0 Hz, 1 H), 2.32 (m, 1 H), 2.19 (m, 1 H), 1.45 (d, br, J = 15.0 Hz, 1 H), 1.34 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 168.08, 164.27, 145.37, 133.50, 130.45, 122.48, 122.04, 111.72, 105.30, 73.60, 68.84, 64.62, 61.93, 56.18, 51.72, 44.65, 43.24, 27.14, 25.02, 20.62; MS: m/z (rel intensity) 354 (M^+ − HI, 3), 296 (5), 282 (9), 239 (7), 221 (7), 206 (5), 194 (11), 180 (18), 172 (8), 167 (9), 157 (13), 151 (16), 142 (100), 127 (59), 115 (14), 106 (8). Anal. Calcd for $C_{21}H_{27}N_2O_3$: C, 52.29; H, 5.64; N, 5.81; I, 26.31. Found: C, 52.04; H, 5.67; N, 5.61; I, 26.10.

(±)-19-*epi*-Alstogustine (5). A solution of 19-*epi*-echitamidine[1,9] (**2**, 20 mg, 0.059 mmol) and iodomethane (4.4 μL, 0.071 mmol) in 1 mL of MeOH was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. Recrystallization from EtOAc/MeOH/Hex gave 26 mg (91%) of (±)-19-*epi*-alstogustine (**5**) as white crystals: mp 164 °C; UV (EtOH) λ_{max} 328, 294, 208 nm; IR (KBr) ν_{max} 3360, 2926, 2842, 1680, 1631, 1606, 1464, 1433, 1379, 1282, 1246, 1199, 1163, 1102, 1016, 915, 728 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.51 (d, J = 7.4 Hz, 1 H), 7.24 (t, J = 7.7 Hz, 1 H), 7.02 (d, J = 7.9 Hz, 1 H), 6.98 (t, J = 7.4 Hz, 1 H), 4.54 (s, 1 H), 3.99 (m, 1 H), 3.87 (m, 1 H), 3.82 (s, 3 H), 3.75 (m, 1 H), 3.74 (dd, J = 6.5, 13.5 Hz, 1 H), 3.52 (dd, J = 11.4, 13.5 Hz, 1 H), 3.50 (s, 3 H), 3.19 (s, br, 1 H), 2.65 (m, 1 H), 2.50 (ddd, J = 3.3, 3.3, 15.0 Hz, 1 H), 2.32 (m, 1 H), 2.14 (m, 1 H), 1.39 (d, br, J = 15.0 Hz, 1 H), 1.30 (d, J = 6.4, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 168.13, 164.32, 145.57, 133.07, 130.43, 122.47, 121.94, 111.76, 104.83, 73.42, 70.61, 64.28, 59.81, 55.85, 51.79, 44.45, 42.62, 28.56, 26.13, 21.62; MS m/z (rel intensity) 354 (M^+, 1), 296 (6), 282 (3), 239 (5), 221 (4), 208 (3), 194 (6), 180 (12), 171 (24), 167 (7), 157 (31), 151 (21), 142 (100), 127 (40), 115 (8), 106 (13). Anal. Calcd for $C_{21}H_{27}N_2O_3$: C, 52.29; H, 5.64; N, 5.81; I, 26.31. Found: C, 52.10; H, 5.52; N, 5.66; I, 26.20.

19-(Benzylthio)akuammicine (15). To a solution of 290 mg (0.747 mmol) of the ketone **4** in 20 mL of glacial HOAc, under Ar, at room temperature, was added 264 μL (2.24 mmol) of benzyl mercaptan, followed by 1.84 mL (14.9 mmol) of $BF_3{\cdot}Et_2O$. The reaction solution was allowed to stir for 20 h and then cooled to 0 °C and basified with concentrated ammonium hydroxide. The aqueous phase was extracted with methylene chloride. The residue obtained upon concentration was purified on a silica gel column, eluting with $CHCl_3$/MeOH (97:3), to give 210 mg of the thio enol ether **15** (63%) and 45 mg of 19-acetoxy 19-thioether **16** (12%) as a white foam, respectively.

For thio enol ether 15: TLC R_f = 0.34 ($CHCl_3$/MeOH, 95:5; CAS blue fade to violet); UV (EtOH) λ_{max} 328, 300, 232, 214 nm; IR (KBr) ν_{max} 3362, 3028, 2946, 1668, 1602, 1464, 1435, 1373, 1239, 1201, 1160, 1103, 1064, 911, 746, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1 H), 7.21−7.11 (m, 7 H), 6.87 (t, J = 7.5 Hz, 1 H), 6.80 (d, J = 7.7 Hz, 1 H), 3.95 (s, 1 H), 3.93 (d, J = 16.0, 1 H), 3.91 (bs, 1 H), 3.85 (d, J = 13.6 Hz, 1 H), 3.80 (s, 3 H), 3.76 (d, J = 13.6 Hz, 1 H), 3.52 (bd, J = 16.0 Hz, 1 H), 3.15 (ddd, J = 5.5, 5.5, 12.6 Hz, 1 H), 2.79 (dd, J = 6.6, 12.6 Hz, 1 H), 2.35 (ddd, J = 2.0, 3.8, 13.5 Hz, 1 H), 2.06 (s, 3 H), 1.79 (ddd, J = 6.6, 6.6, 12.4 Hz, 1 H), 1.55 (dd, J = 5.5, 12.4 Hz, 1 H), 1.23 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.93, 167.67, 143.16, 142.73, 139.14, 137.05, 128.67, 128.42, 127.80, 126.96, 124.77, 121.06, 120.96, 109.41, 100.63, 61.47, 57.42, 56.47, 52.36, 51.04, 46.14, 36.58, 32.17, 31.21, 19.62; MS m/z (rel intensity) 444 (M^+, 5), 353 (25), 321 (11), 243 (10), 242 (17), 216 (17), 156 (17), 152 (31), 128 (19), 124 (17), 111 (13), 91 (100); high-resolution MS, EI ionization, calcd for $C_{27}H_{28}N_2O_2S$ 444.1871, found 444.1867.

For the acetoxy thioether 16: TLC R_f = 0.24 ($CHCl_3$/MeOH, 95:5; CAS light green); UV (EtOH) λ_{max} 330, 298, 226, 204 nm; IR (KBr) ν_{max} 3364, 2947, 1674, 1606, 1465, 1435, 1367, 1240, 1205, 1162, 1104, 1062, 799, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1 H), 7.27 (m, 5 H), 7.14 (m, 2 H), 6.89 (t, J = 7.5 Hz, 1 H), 6.80 (d, J = 7.8 Hz, 1 H), 4.13 (s, 1 H), 4.03 (s, 1 H), 3.89 (d, J = 13.4 Hz, 1 H), 3.84 (d, J = 13.4 Hz, 1 H), 3.78 (m, 1 H), 3.73 (s, 3 H), 3.39 (m, 2 H), 2.91 (dd, J = 6.7, 12.4 Hz, 1 H), 2.22 (bd, J = 13.9 Hz, 1 H), 2.17 (ddd, J = 6.7, 6.7, 13.0 Hz, 1 H), 2.05 (s, 3 H), 1.99 (s, 3 H), 1.77 (dd, J = 6.0, 13.0 Hz, 1 H), 1.29 (bd, J = 13.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.01, 164.44, 143.48, 138.20, 137.19, 135.79, 128.82, 128.32, 128.07, 126.88, 126.73, 121.00, 109.34, 103.42, 60.44, 56.08, 54.86, 50.98, 50.15, 44.30, 36.16, 31.91, 30.38, 22.36, 19.12; MS m/z (rel intensity) 444 (M^+ − OAc, 8), 353 (29), 321 (17), 243 (18), 242 (27), 216 (16), 180 (13), 167 (10), 154 (11), 152 (45), 128 (19), 106 (14), 91 (100).

Regeneration of Ketone 4. To a solution of 15 mg of 19-acetoxy-19-(benzylthio)dihydroakuammicine (**16**) in 2 mL of chloroform, at room temperature, was added 120 μL of CF_3COOH, dropwise. After 4 h, the reaction solution was basified with saturated sodium bicarbonate and extracted with methylene chloride. The residue obtained on concentration was chromatographed on a short silica gel column ($CHCl_3$/MeOH, 9:1) to give 11 mg of ketone **4** (95% yield).

Akuammicine (7). Raney Ni was washed with distilled H_2O to neutral and then with acetone several times. The Raney Ni was left in acetone for 30 min at room temperature, and then it was washed with methanol several times.

To a solution of 15 mg (0.034 mmol) of thio enol ether **15** in 1.5 mL of MeOH at room temperature was added ca. 200 mg of the above treated Raney Ni. The reaction mixture was stirred vigorously for 30 min; then 0.5 mL of Et_3N was introduced and the mixture was stirred for a while. The solids were removed by filtration through Celite and washed with a solution of CH_2Cl_2/MeOH/Et_3N (10:10:1). The filtrate was concentrated in vacuum, and the residue was purified on a silica gel column, eluting with CH_2Cl_2/MeOH (9:1), to give 9 mg of (±)-akuammicine as a white solid (83% yield): TLC R_f = 0.40 ($CHCl_3$/MeOH, 9:1; CAS blue); UV (EtOH) λ_{max} 330, 298, 230, 204 nm; IR (KBr) ν_{max} 3348, 2944, 2924, 2856, 1670, 1603, 1465, 1436, 1373, 1311, 1236, 1200, 1159, 1100, 1055, 789 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1 H), 7.30 (d, J = 7.3 Hz, 1 H), 7.16 (t, J = 7.7 Hz, 1 H), 6.91 (t, J = 7.4 Hz, 1 H), 6.83 (d, J = 7.8 Hz, 1 H), 5.43 (bq, J = 6.9 Hz, 1 H), 4.20 (s, 1 H), 3.99 (d, J = 15.1 Hz, 1 H), 3.97 (s, 1 H), 3.81 (s, 3 H), 3.42 (ddd, J = 5.8, 5.8, 12.5 Hz, 1 H), 3.05 (dd, J = 6.8, 12.5 Hz, 1 H), 3.03 (d, J = 15.1 Hz, 1 H), 2.55 (ddd, J = 6.8, 6.8, 12.7 Hz, 1 H), 2.45 (ddd, J = 2.3, 3.6, 13.7 Hz, 1 H), 1.90 (dd, J = 5.8, 12.7 Hz, 1 H), 1.63 (d, J = 6.9 Hz, 3 H), 1.34 (ddd, J = 2.5, 2.5, 13.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.70, 166.96, 143.30, 137.22, 136.10, 128.08, 122.70, 121.21, 120.93, 109.54, 101.45, 61.46, 56.94, 56.30, 55.49, 51.05, 45.47, 30.46, 29.43, 12.99; MS m/z (rel intensity) 322 (M^+, 22), 263 (4), 252 (4), 220 (4), 216 (5), 206 (6), 193 (4), 180 (5), 167 (6), 154 (4), 121 (100), 106 (10); high-resolution MS, EI ionization, calcd for $C_{20}H_{22}N_2O_2$ 322.1681, found 322.1697. A sample of natural akuammicine gave matching NMR data. It may be noted that previously reported NMR data are not correct, possibly due to use of a salt.[10]

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Supplementary Material Available: Copies of ^1H spectra (for compounds **1**−**7**, **9**, **11**, **12**, **14**−**16**), ^{13}C NMR spectra (for compounds **1**−**7**, **14**−**16**), COSY spectra (for compounds **1**, **3**, **4**, **14**−**16**), and NOESY spectra (for compounds **4** and **15**) (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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