Syntheses of Strychnos- and Aspidospermatan-Type Alkaloids. 5. Total Syntheses of (±)-Echitamidine and 20-*epi*- and 19-*epi*-20-*epi*-Echitamidine

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Intramolecular Diels–Alder reactions, at two stages in the reaction sequence, provided total syntheses of the racemate of the hypotensive alkaloid echitamidine (**8**) and of its C-19,20 and C-20 epimers **9a** and **9b**.

Our development of intramolecular Diels–Alder reactions for generation of strychnos alkaloids (Scheme 1) recently allowed us to report the syntheses of (±)-tubotaiwine (**1**) and (±)-20-*epi*-dihydroakuammicine (**2**), which, in turn, can be epimerized to (±)-dihydroakuammicine (**3**).[1]

The requisite diene enamine precursors **4** and **5** for these syntheses were derived from tetracyclic intermediates **6** and **7** by reductive cleavage of the C/E ring fusion,[2] followed by oxidation and condensation steps as well as manipulation of N^b protecting functionalities. An extension of this methodology to alkaloids of types **2** or **3** with the C-20 ethyl substituent at a higher oxidation level seemed straightforward, but it was found to be somewhat more complicated than anticipated. In this paper we present syntheses of echitamidine (**8**)[3] and of its C-19,20 and C-20 epimers **9a** and **9b**.

The acetyl compound **10** (Scheme 2), which was required for these syntheses, had already been prepared in one of our routes to the aspidosperma alkaloid minovincine,[4] but that preparation was cumbersome. Consequently, we generated the corresponding ethylene glycol derived ketal **11** in one step (92% yield) by condensation of the *N*-benzylindoloazepine **12** with the ketal **13** of formylacetone. While the ketal function was advantageous for the secodine-type 2 + 4 cyclization step leading to the tetracyclic product **11**, and having a masked ketone at C-19 seemed desirable for some of the later steps of our synthesis, the ketal proved to be incompatible with the reductive opening of the tetracycle **11** to an indoloazonine. From the usual conditions of reduction with sodium borohydride in hot acetic acid, the compound was recovered, while more drastic acidic conditions led to mixtures derived from ketal cleavage, ketone reduction, and azonine formation.

The ketal function in **11** was resistant to hydrolysis with hot aqueous HCl, but it could be cleaved with formic and trifluoroacetic acids to provide the ketone **10** (100%). Reduction of this ketone with sodium borohydride in methanol then led to two C-19 epimeric alcohols **14a** and **14b** (1:2, 91%). With addition of $CeCl_3$ in the reduction, only the major epimer **14b** was obtained (96%), while a reduction of the ketone **10** with lithium aluminum hydride or L-Selectride provided equal amounts of the epimeric alcohols **14a** and **14b**. (The stereochemical assignments of these alcohols were established by single-crystal X-ray analysis of the subsequently formed cleavamine **15b**, below.)

The relative C-19, C-20 configuration in the epimer **14a** corresponds to the relative configuration of those centers in echitamidine (**8**). When this tetracyclic alcohol **14a** was subjected to reductive cleavage of the C/E ring juncture with sodium borohydride in hot acetic acid (Scheme 3), two C-16 epimeric indoloazonine esters **15a** and **16a** were obtained (1:1, 94%). The relative configuration at C-16 and C-20 could be obtained from the characteristic difference in chemical shift and coupling constants of the C-16 H (**15a** δ 5.1, d; **16a** δ 5.6, dd).[1]

Hydrogenolysis of the diastereomer **15a**, with carbomethoxy and hydroxyethyl cis substituents, and reaction of the debenzylated amine with di-*tert*-butyl carbonic anhydride, resulted in only a 42% yield of its N-*t*-BOC derivative. However, the same debenzylation conditions with the C-16 epimer **16a**, *t*-BOC protection of the 2° amine **17a**, and acetylation of the resulting alcohol **18a** with acetic anhydride provided the acetate **19a** in 82% overall yield. On heating in toluene with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), the *N*-benzylamine **15a** was converted to its epimer **16a**, thus surmounting the initial synthetic hurdle.

Chlorination of the indole ring of the acetate **19a** with *tert*-butyl hypochlorite and triethylamine, followed by dehydrohalogenation with DBU, then gave the indoloacrylate **20a** (45–53%). N^b-Deprotection of the diene **20a** with trimethylsilyl triflate (100%) produced 2° amine **21a**, the key substrate for introduction of the central two-carbon bridge of the strychnos alkaloid ring system.

Condensation of the amine **21a** with the enol acetate derivative of acetaldehyde, for enamine formation and intramolecular Diels–Alder reaction (analogous to **5**), resulted in pentacyclic product **22a** in variable and modest yields (5–20%). The direction of Diels–Alder addition of the enamine to the diene face with the C-20 substituent followed from that reaction direction, found and predicted by molecular modeling calculation, in the synthesis of 20-*epi*-dihydroakuammicine (**2**).[1]

Methanolysis of the acetate **22a** then provided racemic (±)-3-*epi*-7-*epi*-15-*epi*-echitamidine (**9a**), i.e. (±)-19-*epi*-20-*epi*-echitamidine. On heating this product in methanol at 150 °C, it was equilibrated to (±)-echitamidine (**8**). However, in contrast to the more successful equilibration of (±)-20-*epi*-dihydroakuammicine (**2**) and (±)-dihydroakuammicine (**3**) by this method,[1] the same reaction

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(1) Kuehne, M. E.; Frasier, D. A.; Spitzer, T. *J. Org. Chem.* **1991**, *56*, 2696.

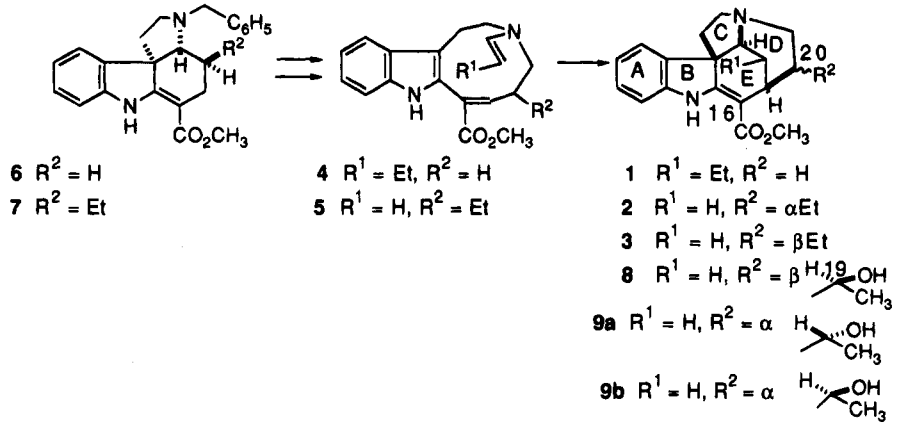
(2) The biogenetic numbering system used for all compounds is that of Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508. Lettering of the fused ring systems follows the same implied principle.

(3) A synthesis of racemic echitamidine was recently reported: Bonjoch, J.; Sole, D.; Bosch, J. *J. Am. Chem. Soc.* **1993**, *115*, 2064.

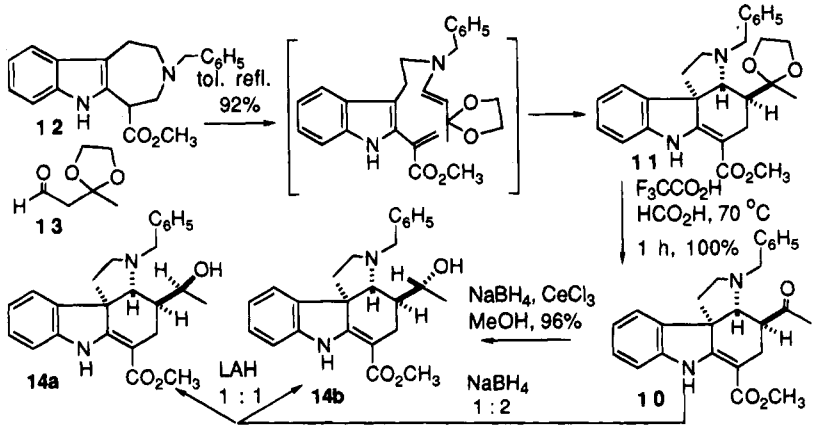
(4) Kuehne, M. E.; Earley, W. G. *Tetrahedron* **1983**, *39*, 3707.

0022-3263/94/1959-5977$04.50/0

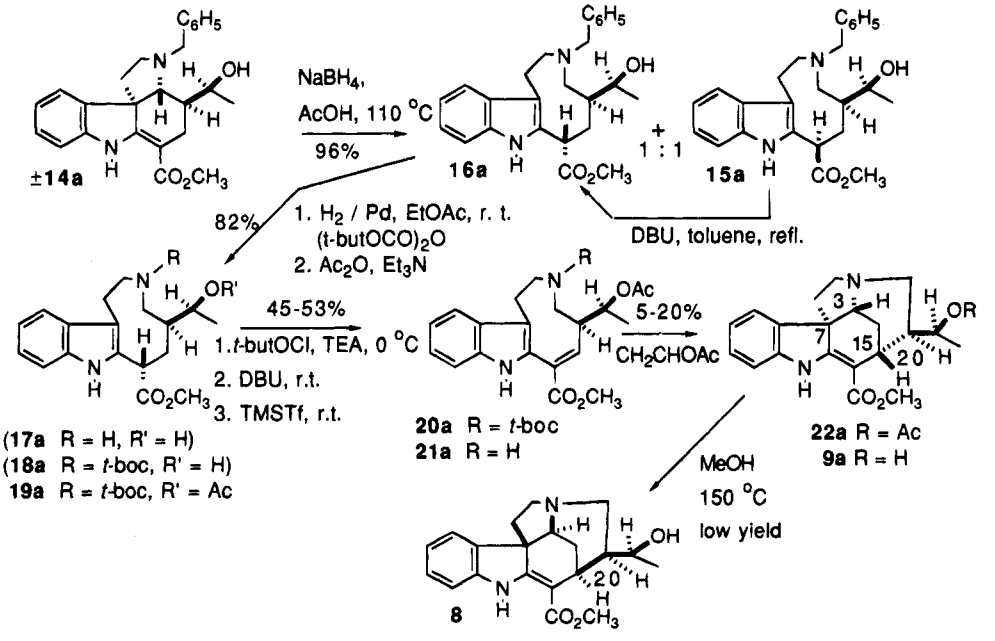
Scheme 1



Scheme 2



Scheme 3



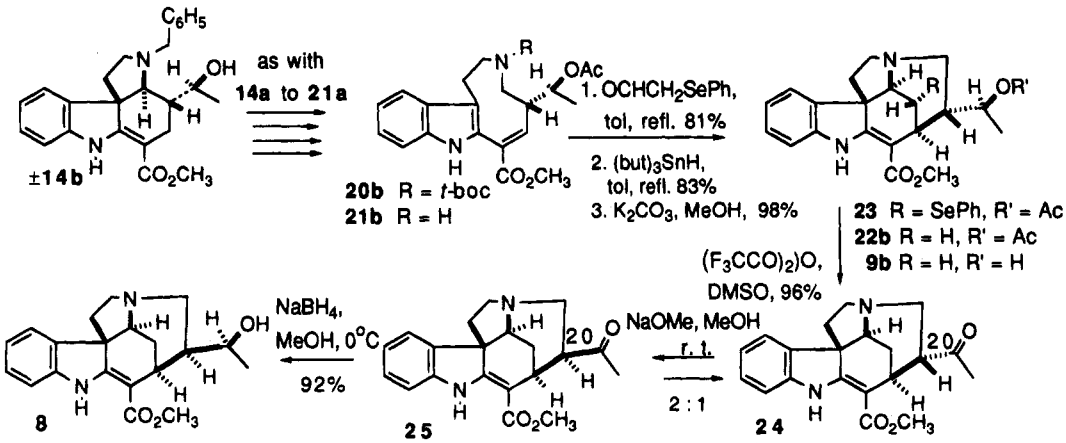
conditions with the 20-hydroxy substituted congener **9a** led mostly to decomposition products.

Three changes in this synthetic strategy were then made to provide substantial improvements in the synthesis of echitamidine (**8**). The initial fixation of the desired C-19,20 relative stereochemistry in precursor **14a** was abandoned. Its selectively formed C-19 epimer **14b** was carried, by the same reaction steps, to formation of the unsaturated indoloazonine **21b** (Scheme 4).

Since our studies with analogous amines had shown that their formation of enamine derivatives, and subsequent intramolecular Diels–Alder reactions, gave best yields with substituted acetaldehydes,[5] the amine **21b** was condensed with (phenylselenyl)acetaldehyde[6] to furnish 14-(phenylselenyl)-20-*epi*-echitamidine acetate

(5) Kuehne, M. E.; Brook, C. S.; Frasier, D. A. *Nat. Prod. Lett.* **1994**, *4*, 65.
(6) Baudat, R.; Petrzilka, M. *Helv. Chim. Acta* **1979**, *62*, 1406.

Scheme 4



(**23**, 81%). Reductive cleavage of the selenyl ether function with tributyltin hydride (83%) and methanolysis of the resulting acetate **22b** (98%) provided (±)-20-*epi*-echitamidine (**9b**).

In order to achieve epimerization at C-20, the alcohol **9b** was subjected to a modified Swern oxidation and the resulting ketone **24** (96%) was then treated with sodium methoxide. A 1:2 ratio of epimeric ketones **24** and **25** was obtained. Reduction of the latter product with sodium borohydride gave only (±)-echitamidine (**8**, 92%).

Comparison of ^{1}H NMR data for the alcohols **9a** and **9b** with those of the other known natural echitamidine diastereomer[7] now enabled a relative configuration assignment to that alkaloid as **9a** (19-*epi*-20-*epi*-echitamidine).

Experimental Section

(±)-Methyl 3-Benzyl-4-(2-(2-methyl-1,3-dioxolanyl))-1,2,3,3a,4,5-hexahydro-7*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (11). A solution of N^b-benzylindoloazepine **12** (1.7 g, 4.5 mmol) and 2-(2-(2-methyl-1,3-dioxolanyl))ethanal[8] (0.70 g, 5.4 mmol) in 200 mL of dry toluene was heated at reflux for 36 h using a Dean–Stark trap filled with 4 Å molecular sieves. The reaction mixture was cooled and then concentrated on a rotary evaporator. Flash chromatography on silica gel, eluting with CH_2Cl_2/ether (3:1), gave 2.03 g (92%) of **11**: mp 144–145 °C; TLC (SiO_2, CH_2Cl_2:ether = 1:1) R_f = 0.52 (CAS, dark blue); 270-MHz ^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1 H), 7.41–7.25 (m, 5 H), 7.11–7.05 (m, 1 H), 6.78–6.73 (m, 3 H), 4.16 (d, 1 H, J = 14 Hz), 3.78 (s, 3H), 3.78–3.59 (m, 4 H), 3.58–3.52 (m, 1 H), 3.27 (s, 1 H), 3.11 (q, 1 H, J = 7 Hz), 3.00–2.86 (m, 2 H), 2.71–2.55 (m, 1 H), 2.20 (s, 1 H), 2.02–1.98 (m, 1 H), 1.67 (dd, 1 H, J = 4, 7 Hz), 1.07 (s, 3 H); 67.5-MHz ^{13}C NMR ($CDCl_3$) δ 168.8, 167.5, 143.3, 138.6, 138.2, 129.2, 128.2, 127.4, 126.9, 121.7, 120.2, 111.2, 108.9, 89.8, 66.5, 64.7, 63.6, 56.8, 55.8, 50.8, 49.8, 46.9, 41.8, 23.1, 20.2; IR (film) ν_{max} 3377 (m), 3058 (w), 3027 (w), 2976 (m), 2943 (m), 2905 (m), 2878 (m), 2792 (w), 1676 (s), 1609 (s), 1475 (m), 1465 (s), 1435 (m), 1371 (m), 1342 (m), 1292 (m), 1276 (s), 1248 (s), 1209 (m), 1194 (s), 1120 (s), 1081 (m), 1046 (s) cm^{-1}; UV (ethanol) λ_{max} 326, 300, 226, 204 nm; MS *m/e* (relative intensity) 446 (M^+, 4), 232 (17), 227 (8), 134 (6), 91 (45), 88 (5), 87 (100). Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.43; H, 6.80; N, 6.05.

(±)-Methyl 4-Acetyl-3-benzyl-1,2,3,3a,4,5-hexahydro-7*H*-pyrrolo[2,3-*d*]carbazole-6-carboxylate (10). The cyclic ketal **11** (0.82 g, 1.8 mmol) was dissolved in 2 mL of trifluoroacetic acid. Wet formic acid (75 mL) was added and the mixture immersed in a 70 °C oil bath for 1 h. The reaction mixture was poured over crushed ice, basified with NH_4OH, and then extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were dried over magnesium sulfate and then concentrated on a rotary evaporator. Flash chromatography on silica gel, eluting with CH_2Cl_2/ether (3:1), gave 0.736 g (100%) of **10**, which has been made previously in the group by a different method.[4]

(±)-(3a*R,4*S**,11bS*,1′*S**(and 1′*R**)-Methyl 3-Benzyl-4-(1-(1-hydroxyethyl))-1,2,3,3a,4,5-hexahydro-7*H*-pyrrolo-[2,3-*d*]carbazole-6-carboxylate (14a and 14b). a.** To a solution of **10** (0.2 g, 0.5 mmol) in 10 mL of dry THF cooled to −78 °C was added lithium aluminum hydride (0.546 mL, 1.0 M in hexane) via syringe. The reaction mixture was stirred for 30 min, warmed to room temperature, quenched with 5% HCl, basified with NH_4OH, and extracted with CH_2Cl_2 (3 × 100 mL). The organic phase was dried with sodium sulfate and then concentrated on a rotary evaporator. Flash chromatography on silica gel, eluting with ether/hexane (7:3), gave 0.183 g (91%) of a 1:1 mixture of **14a** and **14b**.

For 14b: mp 155–157 °C; TLC (SiO_2, ether/hexane = 7:3) R_f = 0.23 (CAS, dark blue); 270-MHz ^{1}H NMR ($CDCl_3$) δ 8.91 (s, 1 H), 7.42–7.23 (m, 5 H), 7.09 (t, 1 H), 6.84–6.74 (m, 3 H), 4.14 (d, 1 H, J = 13 Hz), 3.77 (d, 1 H, J = 13 Hz), 3.75 (s, 3 H), 3.54 (s, 1 H), 3.17 (t, 1 H), 2.91 (t, 1 H), 2.75–2.66 (m, 2 H), 2.52 (dd, 1 H, J = 15, 3 Hz), 2.05 (dq, 1 H, J = 6 Hz), 1.74–1.61 (m, 2 H), 1.25 (bs, 1 H), 1.06 (d, 3 H, J = 6 Hz); 67.5-MHz ^{13}C NMR ($CDCl_3$) δ 168.4, 165.4, 142.9, 138.7, 137.9, 129.1, 128.1, 127.7, 126.9, 122.4, 120.7, 109.0, 90.4, 67.3, 66.8, 57.2, 55.4, 50.8, 50.0, 48.0, 42.0, 22.2, 20.8; IR (film) ν_{max} 3383 (m), 3055 (w), 3027 (w), 2964 (m), 2946 (m), 2903 (m), 2861 (m), 2794 (w), 1672 (s), 1608 (s), 1476 (m), 1461 (s), 1450 (m), 1435 (s), 1373 (w), 1302 (m), 1292 (m), 1278 (s), 1246 (s), 1203 (s), 1134 (s), 1117 (m), 1100 (s), 1076 (m), 1048 (s), 1013 (m) cm^{-1}; UV (ethanol) λ_{max} 328, 300, 226, 206 nm; MS *m/e* (relative intensity) 404 (M^+, 3), 271 (23), 227 (5), 194 (10), 191 (9), 190 (83), 168 (6), 166 (14), 154 (8), 146 (7), 134 (8), 92 (5), 91 (100), 82 (26). Anal. Calcd for $C_{25}H_{28}N_2O_3$ and 1 equiv of diethyl ether: C, 72.77; H, 8.00; N, 5.85. Found: C, 73.14; H, 8.00; N, 5.75.

For 14a: TLC (SiO_2, ether/hexane = 7:3) R_f = 0.14 (CAS, dark blue); 270-MHz ^{1}H NMR ($CDCl_3$) δ 8.89 (s, 1 H), 7.40–7.24 (m, 5 H), 7.14 (t, 1 H), 7.00 (d, 1 H), 6.87–6.78 (m, 2 H) 4.12 (d, 1 H, J = 13 Hz), 3.78 (s, 3 H), 3.72 (d, 1 H, J = 13 Hz), 3.24 (t, 1 H), 3.02 (s, 1 H), 2.96–2.88 (m, 2 H), 2.70–2.60 (m, 1 H), 2.48 (dd, 1 H, J = 15, 3 Hz), 2.07 (dq, 1 H, J = 6 Hz), 1.88 (d, 1 H), 1.04 (d, 3 H, J = 6 Hz); 67.5-MHz ^{13}C NMR ($CDCl_3$) δ 168.5, 165.0, 142.9, 138.9, 137.6, 128.8, 128.2, 127.8, 127.0, 122.1, 120.6, 109.2, 90.6, 68.3, 66.4, 57.7, 55.5, 51.0, 50.2, 47.6, 41.9, 21.1, 20.1; IR (film) ν_{max} 3377 (m), 3054 (w), 3027 (w), 2964 (m), 2949 (m), 2905 (m), 2855 (m), 2794 (w), 1674 (s), 1608 (s), 1492 (w), 1476 (m), 1463 (s), 1451 (m), 1435 (s), 1377 (w), 1341 (w), 1302 (m), 1291 (m), 1277 (s), 1249 (s), 1204 (s), 1130 (m), 1100 (m), 1090 (m), 1050 (w), 1015 (w) cm^{-1}; UV (ethanol) λ_{max} 328, 300, 228, 204 nm; MS *m/e* (relative

(7) Zeches, M.; Ravao, T.; Richard, B.; Massiot, G.; Le Men-Olivier, L.; Guilhem, J.; Pascard, C. *Tetrahedron Lett.* **1984**, *25*, 659.

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

intensity) 404 (M^+, 3), 271 (24), 227 (5), 194 (9), 191 (9), 190 (84), 168 (5), 166 (14), 154 (7), 146 (7), 134 (8), 92 (5), 91 (100), 82 (25); HRMS M + 1^+ calcd 405.21782, found 405.2178.

b. To a solution of **10** (71 mg, 0.18 mmol) in 5 mL of dry methanol was added $CeCl_3$ (78 mg, 0.209 mmol), and the temperature of the mixture was lowered to −20 °C. $NaBH_4$ (34 mg, 0.898 mmol) was added in small portions. The reaction was quenched with 5% HCl, poured over crushed ice, made strongly basic with NH_4OH, and then extracted with CH_2Cl_2 (3 × 100 mL). The organic phase was dried with sodium sulfate and then concentrated by rotary evaporator. Flash chromatography on silica gel, eluting with ether/hexane (7:3), gave 68 mg (96%) of **14b**.

(±)-(5*S,1′*S**,7*R**(and 7*S**)-3-Benzyl-5-(1-(1-hydroxyethyl))-7-(methoxycarbonyl)-1,2,3,4,5,6,7,8-octahydroindolo-[3,2-*d*]azonine (15a and 16a).** The tetracyclic alcohol **14a** (0.381 g, 0.942 mmol) was dissolved in 40 mL of glacial acetic acid and heated to 110 °C with an oil bath. $NaBH_4$ (0.356 g, 9.42 mmol) was added in small portions over a period of 15 min. The reaction mixture was poured over crushed ice, made basic with NH_4OH, and then extracted with CH_2Cl (4 × 50 mL). The organic phase was dried with sodium sulfate and then concentrated on a rotary evaporator. Flash chromatography on silica gel, eluting with CH_2Cl_2/ether (1:1), gave 0.37 g (96%) of a 1:1 mixture of the diastereomers **15a** and **16a**.

For 15a: TLC (SiO_2, CH_2Cl_2:ether = 1:1) R_f = 0.30 (CAS, green); 270-MHz ^1H NMR ($CDCl_3$) δ 8.62 (s, 1 H), 7.43−7.05 (m, 9 H), 5.01 (d, 1 H, J = 9 Hz), 3.81 (d, 1 H, J = 14 Hz), 3.72 (s, 3 H), 3.65 (m, 1 H), 3.35 (d, 1 H, J = 14 Hz), 2.84−2.64 (m, 2 H), 2.41−2.30 (m, 3 H), 2.25 (m, 2 H), 1.90−1.80 (m, 1 H), 1.70−1.55 (m, 1 H), 1.03 (d, 3 H, J = 6 Hz); 67.5-MHz ^{13}C NMR ($CDCl_3$) δ 175.2, 140.2, 136.1, 133.6, 128.7, 128.3, 127.8, 126.9, 121.7, 119.1, 118.2, 111.9, 110.8, 70.9, 61.3, 57.1, 52.6, 52.2, 45.3, 40.5, 33.0, 26.3, 20.0; IR (film) ν_{max} 3435 (m), 3385 (m), 3085 (w), 3059 (w), 3026 (w), 2967 (m), 2947 (m), 2928 (m), 2887 (m), 2843 (m), 2823 (m), 1717 (s), 1492 (m), 1459 (s), 1433 (s), 1369 (m), 1337 (s), 1306 (m), 1283 (s), 1242 (s), 1195 (m), 1163 (s), 1144 (m), 1130 (m), 1054 (m), 1024 (m) cm^{-1}; UV (ethanol) λ_{max} 292, 284, 228, 208 nm; MS *m/e* (relative intensity) 407 (M + 1^+, 6), 406 (M^+, 23), 215 (14), 204 (9), 202 (16), 190 (11), 169 (11), 134 (17), 133 (20), 132 (15), 120 (12), 91 (100), 86 (13), 85 (11), 84 (33), 71 (15).

For 16a: TLC (SiO_2, CH_2Cl_2:ether = 1:1) R_f = 0.50 (CAS, green); 270-MHz ^1H NMR ($CDCl_3$) δ 8.72 (s, 1 H), 7.45−7.02 (m, 9 H), 5.55 (dd, 1 H, J = 5, 7 Hz), 3.85 (d, 1 H, J = 13 Hz), 3.77 (s, 3 H), 3.72 (d, 1 H, J = 13 Hz), 3.49−3.46 (m, 1 H), 2.91−2.37 (m, 6 H), 2.03 (m, 1 H), 1.71−1.61 (m, 1 H), 1.09 (m, 2 H), 0.95 (d, 3 H, J = 6 Hz); 67.5-MHz ^{13}C NMR ($CDCl_3$) δ 175.9, 139.6, 135.8, 131.5, 129.4, 128.2, 128.0, 126.9, 121.4, 118.9, 117.8, 114.6, 110.8, 70.3, 63.2, 58.1, 55.8, 52.1, 41.5, 40.6, 35.0, 24.8, 20.4; IR (film) ν_{max} 3390 (m), 3057 (w), 3025 (w), 2971 (m), 2945 (m), 2919 (m), 2846 (m), 2820 (m), 2795 (m), 1717 (s), 1490 (w), 1459 (s), 1433 (m), 1337 (m), 1316 (m), 1251 (m), 1210 (m), 1185 (m), 1161 (s), 1128 (m), 1075 (s), 1022 (m), 907 (m) cm^{-1}; UV (ethanol) λ_{max} 292, 282, 230, 210 nm; MS *m/e* (relative intensity) 407 (M + 1^+, 4), 406 (M^+, 19), 215 (12), 204 (9), 202 (17), 190 (11), 169 (11), 134 (16), 133 (25), 132 (16), 120 (10), 91 (90), 86 (13), 85 (11), 84 (100), 71 (31); HRMS calcd for $C_{25}H_{30}N_2O_3$ M + 1^+ 407.2335, found 407.2335.

To a solution of the alcohol **15a** (88 mg, 0.22 mmol) in 20 mL of toluene was added one drop of diazabicycloundecene. The solution was heated at reflux for 24 h and then concentrated to dryness and the residue chromatographed on silica gel, eluting with dichloromethane/ether (3:1). An 8:2 mixture of diastereomers **16a**:**15a** (87 mg, 99%) was obtained.

(±)-(5*S,1′*R*,7*R**(and 7*S**)-3-Benzyl-5-(1-(1-hydroxyethyl))-7-(methoxycarbonyl)-1,2,3,4,5,6,7,8-octahydroindolo-[3,2-*d*]azonine (15b and 16b).** The tetracyclic alcohol **14b** (1.04 g, 2.57 mmol) was reduced with $NaBH_4$ (1.13 g, 24.7 mmol) according to the preceding procedure. The crude product was purified by flash chromatography on silica gel. Elution with CH_2Cl_2/ether (1:1) gave 0.97 g (94%) of a 1:1 mixture of the diastereomers **15b** and **16b**.

For 15b: TLC (SiO_2, CH_2Cl_2:ether = 1:1) R_f = 0.32 (CAS, green); 270-MHz ^1H NMR ($CDCl_3$) δ 8.73 (s, 1 H), 7.43−7.02 (m, 9 H), 5.06 (d, 1 H, J = 9 Hz), 3.81 (d, 1 H, J = 14 Hz), 3.72 (s, 3 H), 3.51 (t, 1 H, J = 6 Hz), 3.35 (d, 1 H, J = 14 Hz), 2.83−2.70 (m, 3 H), 2.38−2.24 (m, 4 H), 2.09 (q, 1 H, J = 9 Hz), 1.89 (m, 1 H), 1.61 (s, 1 H), 1.04 (d, 3 H, J = 6 Hz); 67.5-MHz ^{13}C NMR ($CDCl_3$) δ 175.3, 140.2, 136.1, 133.7, 128.6, 128.2, 127.8, 126.8, 121.6, 119.1, 118.1, 111.8, 110.8, 70.5, 60.9, 55.7, 52.5, 52.2, 45.6, 40.3, 34.3, 26.2, 20.1; IR (film) ν_{max} 3440 (m), 3380 (m), 3083 (w), 3056 (w), 3026 (w), 2949 (m), 2927 (m), 2843 (m), 1717 (s), 1601 (w), 1491 (m), 1461 (s), 1448 (s), 1433 (s), 1369 (m), 1336 (m), 1302 (m), 1283 (s), 1242 (s), 1203 (s), 1162 (s), 1130 (m), 1069 (m), 1048 (m), 1022 (m) cm^{-1}; UV (ethanol) λ_{max} 292, 284, 274, 224, 206 nm; MS *m/e* (relative intensity) 406 (M^+, 12), 261 (10), 255 (5), 215 (25), 204 (15), 202 (29), 190 (14), 169 (11), 156 (16), 134 (19), 133 (28), 132 (28), 119 (18), 91 (100). Anal. Calcd for $C_{25}H_{30}N_2O_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 73.79; H, 7.51; N, 6.80.

For 16b: TLC (SiO_2, CH_2Cl_2:ether = 1:1) R_f = 0.47 (CAS, green); 270-MHz ^1H NMR ($CDCl_3$) δ 8.79 (s, 1 H), 7.45−7.21 (m, 7 H), 7.13−7.04 (m, 2 H), 5.58 (dd, 1 H, J = 5, 12 Hz), 3.84 (d, 1 H, J = 13 Hz), 3.76 (s, 3 H), 3.67 (d, 1 H, J = 13 Hz), 3.43 (m, 1 H), 2.93−2.80 (m, 2 H), 2.62−2.35 (m, 4 H), 2.04 (m, 1 H), 1.65 (m, 1 H), 1.25 (m, 1 H), 1.06 (m, 1 H), 0.88 (d, 3 H, J = 6 Hz); 67.5-MHz ^{13}C NMR ($CDCl_3$) δ 175.8, 139.5, 135.7, 131.4, 129.4, 128.2, 128.0, 127.0, 121.3, 118.9, 117.8, 114.6, 110.8, 70.0, 63.3, 57.5, 55.9, 52.1, 41.7, 40.5, 35.4, 24.8, 19.4; IR (film) ν_{max} 3546 (w), 3396 (m), 3082 (w), 3056 (w), 3026 (m), 2967 (m), 2919 (m), 2850 (m), 2804 (m), 1720 (s), 1599 (w), 1491 (m), 1459 (s), 1434 (s), 1362 (m), 1336 (m), 1287 (m), 1250 (s), 1209 (m), 1192 (m), 1160 (s), 1128 (m), 1065 (w), 1022 (m) cm^{-1}; UV (ethanol) λ_{max} 292, 284, 274, 224, 204 nm; MS *m/e* (relative intensity) 406 (M^+, 15), 261 (10), 215 (30), 204 (12), 202 (36), 190 (12), 169 (11), 156 (17), 144 (14), 134 (19), 133 (33), 132 (34), 120 (20), 91 (100); HRMS calcd for $C_{25}H_{30}N_2O_3$ M + 1^+ 407.23347, found 407.2335.

To a solution of the alcohol **15b** (47 mg, 0.12 mmol) in 20 mL of toluene was added one drop of diazabicycloundecene. The solution was heated at reflux for 24 h and then concentrated to dryness and the residue chromatographed on silica gel, eluting with dichloromethane/ether (3:1) to provide 43 mg (91%) of the diastereomer **16b**.

(±)-(5*S,1′*S**,7*S**)-3-(*tert*-Butoxycarbonyl)-5-(1-(1-acetoxyethyl))-7-(methoxycarbonyl)-1,2,3,4,5,6,7,8-octahydroindolo[3,2-*d*]azonine (19a).** The cleavamine alcohol **16a** (0.176 g, 0.433 mmol) and di-*tert*-butyl carbonic anhydride (0.113 g, 0.52 mmol) were dissolved in 40 mL of ethyl acetate. To this mixture was added 0.06 g of 10% Pd/C, and the reaction was stirred for 18 h under 1 atm of H_2. The reaction mixture was filtered through a plug of Celite, and triethylamine (0.603 ml, 4.33 mmol) and acetic anhydride (0.204 mL, 2.165 mmol) were added. The reaction was monitored by TLC; when complete, the mixture was washed with water and the organic phase was dried with sodium sulfate and then concentrated on a rotary evaporator. Flash chromatography on silica gel, eluting with ether/hexane (7:3), gave 0.167 g (82%) of **19a**: TLC (SiO_2, ether/hexane = 7:3) R_f = 0.35 (CAS, green); 270-MHz ^1H NMR ($CDCl_3$) δ 8.73 (s, 1 H), 7.53 (t, 1 H, J = 7 Hz), 7.35 (d, 1 H, J = 7 Hz), 7.20−7.11 (m, 2 H), 4.61 (bs, 1 H), 4.19−4.09 (m, 2 H), 3.75/3.71 (s, 3 H), 3.28−2.85 (m, 2 H), 2.62−2.54 (m, 2 H), 2.13−2.07 (m, 2 H), 1.97/1.96 (s, 3 H), 1.57/1.55 (s, 9 H), 1.26 (bs, 2 H), 1.03 (d, 3 H, J = 6 Hz); 67.5-MHz ^{13}C NMR ($CDCl_3$) 34 peaks due to rotomers; IR (film) ν_{max} 3382 (m), 2973 (m), 2950 (m), 2931 (m), 1735 (s), 1688 (s), 1461 (s), 1437 (m), 1414 (s), 1388 (w), 1365 (s), 1337 (m), 1302 (m), 1240 (s), 1167 (s), 1130 (m), 1112 (w), 1050 (m), 1022 (w), 909 (w) cm^{-1}; UV (ethanol) λ_{max} 292, 282, 274, 224, 202 nm; MS *m/e* (relative intensity) 458 (M^+, 9), 310 (9), 297 (5), 215 (9), 214 (14), 144 (6), 58 (5), 57 (100).

(±)-(5*S,1′*S**,7*S**)-3-(*tert*-Butoxycarbonyl)-5-(1-(1-acetoxyethyl))-7-(methoxycarbonyl)-1,2,3,4,5,6,7,8-octahydroindolo[3,2-*d*]azonine (19b).** The cleavamine alcohol **16b** (0.11 g, 0.271 mmol) was debenzylated and deprotected according to the preceding procedure for the epimer **16a**. The crude reaction mixture was purified by flash chromatography on silica gel. Elution with ether/hexane (7:3) gave 0.107 g (86%) of **19b**: TLC (SiO_2, ether/hexane = 7:3) R_f = 0.35 (CAS, green); 270-MHz ^1H NMR ($CDCl_3$) δ 8.73 (s, 1 H), 7.53 (t, 1 H, J = 7 Hz), 7.35 (d, 1 H, J = 7 Hz), 7.20−7.11 (m, 2 H), 4.61

(bs, 1 H), 4.19–4.09 (m, 2 H), 3.75/3.71 (s, 3 H), 3.28–2.85 (m, 2 H), 2.62–2.54 (m, 2 H), 2.13–2.07 (m, 2 H), 1.97/1.96 (s, 3 H), 1.57/1.55 (s, 9 H), 1.26 (bs, 2 H), 1.03 (d, 3 H, J = 6 Hz); 67.5-MHz ^{13}C NMR ($CDCl_3$) 36 peaks due to rotamers; IR (film) ν_{max} 3376 (m), 2973 (m), 2929 (m), 2857 (w), 1735 (s), 1687 (s), 1461 (s), 1440 (m), 1414 (s), 1389 (m), 1365 (s), 1339 (m), 1307 (s), 1241 (s), 1167 (s), 1017 (m), 962 (m) cm^{-1}; UV (ethanol) λ_{max} 292, 284, 276, 224, 204 nm; MS *m/e* (relative intensity) 458 (M^+, 69), 402 (69), 357 (65), 328 (70), 310 (100), 297 (61), 215 (53), 214 (90); HRMS calcd for $C_{25}H_{34}N_2O_6$ M^+ 458.24169, found 458.2417.

(±)-(5S*,1′S*,7S*)-3-(*tert*-Butoxycarbonyl)-5-(1-(1-acetoxyethyl))-7-(methoxycarbonyl)-1,2,3,4,5,8-hexahydroindolo[3,2-*d*]azonine (20b). A solution of *t*-BOC cleavamine **19b** (0.101 g, 0.22 mmol) in 25 mL of dry CH_2Cl_2 and triethylamine (0.037 mL, 0.26 mmol) was cooled to 0 °C. *tert*-Butyl hypochlorite (0.027 mL, 0.242 mmol) was added, and the reaction mixture was stirred for 15 min. The mixture was washed with brine, dried over sodium sulfate, and concentrated under vacuum to give a white foam. This chloroindolenine was stirred at room temperature in 50 mL of dry CH_2Cl_2 with DBU (0.072 mL, 0.484 mmol) for 1 h. The reaction mixture was concentrated on a rotary evaporator. Flash chromatography on silica gel, eluting with ether/hexane (7:3), gave 47 mg (46%) of **20b**: TLC (SiO_2, ether/hexane = 7:3) R_f = 0.3 (CAS, green); 500-MHz ^{1}H NMR ($CDCl_3$) δ 8.09/8.05 (s, 1 H), 7.59–7.54 (m, 1 H), 7.35–7.07 (m, 4 H), 4.91–4.84 (m, 1 H), 4.12–3.80 (m, 2 H), 3.72 (s, 3 H), 2.99–2.75 (m, 3H), 2.59–2.51 (m, 2 H), 1.97/1.95 (s, 3 H), 1.49/1.43 (s, 9 H), 1.11/1.09 (d, 3 H, J = 6 Hz); 125-MHz ^{13}C NMR ($CDCl_3$) 47 peaks due to rotamers; IR (film) ν_{max} 3384 (m), 2972 (m), 2927 (m), 2858 (w), 1733 (s), 1717 (s), 1688 (s), 1461 (m), 1441 (m), 1414 (m), 1363 (m), 1337 (m), 1306 (m), 1259 (m), 1234 (m), 1165 (s), 1132 (m) cm^{-1}; UV (ethanol) λ_{max} 298, 284, 278, 222, 208 nm; MS *m/e* (relative intensity) 456 (M^+, 5), 340 (10), 295 (10), 241 (10), 57 (100); HRMS calcd for $C_{25}H_{32}N_2O_6$ M^+ 456.22604, found 456.2260.

(±)-19-*epi*-20-*epi*-Echitamidine Acetate (22a). A solution of *t*-BOC cleavamine **19a** (62 mg, 0.135 mmol) in CH_2Cl_2 and 24 μL (0.175 mmol) of triethylamine was cooled to 0 °C. *tert*-Butyl hypochlorite (17 μL, 0.15 mmol) was added, and the reaction mixture was stirred for 10 min. Then 1,8-diazabicyclo-[5.4.0]undec–7–ene (DBU, 40 μL, 0.27 mmol) was added and the mixture stirred for 30 min at room temperature. The resulting crude *t*-BOC cleavamine diene **20a** was deprotected by the addition of trifluoroacetic acid (104 μL, 1.35 mmol); then the mixture was poured over crushed ice, basified with potassium carbonate, and extracted with CH_2Cl_2 (3 × 50 mL). The organic phases were dried with sodium sulfate and then concentrated on a rotary evaporator. The yellow residue (**21a**) was then taken up in 50 mL of $CHCl_3$. Triethylamine (188 μL, 1.35 mmol) and vinyl acetate (124 μL, 1.35 mmol) were added, and the mixture was heated at reflux for 36 h. Concentration on a rotary evaporator followed by flash chromatography on silica gel, eluting with ethyl acetate/ethanol/triethylamine (48:2:1), gave 9.3 mg (18%, but variable 5–20%) of product **22a**: TLC (SiO_2, ethyl acetate/ethanol/triethylamine = 48:2:1) R_f = 0.16 (CAS, dark blue); 500-MHz ^{1}H NMR ($CDCl_3$) δ 8.86 (s, 1 H), 7.20 (d, 1 H, J = 7.3 Hz), 7.14 (t, 1 H, J = 7.6 Hz), 6.89 (t, 1 H, J = 7.5 Hz), 6.81 (d, 1 H, J = 7.6 Hz), 4.88 (m, 1 H), 4.04 (bs, 1 H), 3.78 (s, 3 H), 3.22–3.20 (m, 1 H), 3.08 (bs, 1 H), 3.02–2.96 (m, 2 H), 2.63 (dd, 1 H, J = 6.0, 14.2 Hz), 2.34–2.28 (m, 1 H), 2.21 (dt, 1 H, J = 3.1, 13.7 Hz), 2.07 (s, 3 H), 2.06–1.98 (m, 2 H), 1.28 (d, 3 H, J = 6.4 Hz), 1.17 (dt, 1 H, J = 2.8, 13.7, Hz); 125-MHz ^{13}C NMR ($CDCl_3$) δ 170.7, 167.8 (two signals), 144.0, 135.4, 127.8, 120.9, 120.7, 109.5, 103.7, 72.3, 58.9, 58.0, 53.6, 51.0, 47.9, 45.6, 41.3, 27.5, 27.3, 27.0, 21.3; IR (film) ν_{max} 3361 (m), 2945 (m), 2931 (m), 2856 (m), 1730 (s), 1673 (s), 1603 (s), 1475 (m), 1464 (s), 1434 (m), 1369 (m), 1307 (w), 1281 (m), 1242 (s), 1197 (s), 1163 (m), 1099 (m), 1054 (w) cm^{-1}; UV (ethanol) λ_{max} 326, 300, 226, 204 nm; MS *m/e* (relative intensity) 383 (M + 1^+, 13), 382 (M^+, 59), 227 (20), 225 (89), 194 (26), 193 (22), 181 (20), 180 (33), 167 (35), 121 (99), 98 (100), 97 (27), 77 (25).

(±)-19-*epi*-20-*epi*-Echitamidine (9a). 19-*epi*-20-*epi*-Echitamidine acetate (**22a**) (17 mg, 0.044 mmol) was dissolved in 10 mL of methanol, and 1 mL of satd potassium carbonate was added. The reaction mixture was stirred for 18 h. The methanol was evaporated and the aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL). The organic phase was dried over sodium sulfate and concentrated on a rotary evaporator. Purification by flash chromatography, eluting with ethyl acetate/ethanol/triethylamine (40:10:2), gave 13 mg (87%) of **9a**.

For **9a**: mp 168–9 °C (recrystallized from MeOH/EtOAc/hexanes); 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}; ^{1}H 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, 46.69, 45.37, 29.19, 27.24, 20.17; MS *m/z* (relative 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.

(±)-14-(Phenylselenyl)-20-*epi*-Echitamidine Acetate (23). To a solution of *t*-BOC cleavaminediene **20b** (41 mg, 0.090 mmol) in 10 mL of dry CH_2Cl_2 and triethylamine (26 μL, 0.19 mmol) was added trimethylsilyl trifluoromethanesulfonate (36 μL, 0.19 mmol), and the reaction mixture was stirred for 1 h at room temperature. The mixture was washed with 5% sodium bicarbonate, dried over sodium sulfate, and concentrated under vacuum to give a clear film. This deprotected cleavamine diene (**21b**) was dissolved in 25 mL of dry toluene, and (phenylselenyl)acetaldehyde[6] (27 mg, 0.135 mmol) was added. The reaction mixture was stirred at room temperature and monitored by TLC. When all of the starting material had been consumed, the mixture was heated at reflux for 6 h. Concentration on a rotary evaporator, followed by flash chromatography on silica gel, eluting with ethyl acetate/triethylamine (10:0.4), gave 38 mg (81%) of **23**: TLC (SiO_2, ethyl acetate/triethylamine = 10:0.4) R_f = 0.26 (CAS, dark blue); 500-MHz ^{1}H NMR ($CDCl_3$) δ 9.09 (s, 1 H), 7.35 (d, 1 H, J = 7.5 Hz), 7.31–7.19 (m, 6 H), 6.97 (t, 1 H, J = 7.5 Hz), 6.92 (d, 1 H, J = 7.6 Hz), 5.00–4.97 (m, 1 H), 4.27 (bs, 1 H), 3.95 (t, 1 H, J = 3.1 Hz), 3.82 (s, 3 H), 3.26–3.22 (m, 2 H), 3.11 (dd, 1 H, J = 11.9, 14.4 Hz), 3.08–3.03 (m, 1 H), 2.73 (dd, 1 H, J = 6.0, 14.4 Hz), 2.33–2.26 (m, 2 H), 2.06–2.00 (m, 1 H), 2.01 (s, 3 H), 1.29 (d, 3 H, J = 6.3 Hz); 125-MHz ^{13}C NMR ($CDCl_3$) δ 170.5, 168.9, 167.9, 143.2, 136.8, 134.9, 129.2, 128.9, 127.7, 127.6, 121.2, 120.4, 109.8, 98.8, 73.6, 64.8, 58.0, 54.1, 51.1, 46.4, 45.4, 44.8, 43.8, 35.5, 21.1, 17.4; IR (film) ν_{max} 3360 (m), 2948 (m), 2931 (m), 2853 (m), 1731 (s), 1672 (s), 1602 (s), 1474 (m), 1463 (m), 1435 (m), 1371 (m), 1279 (m), 1242 (s), 1193 (s), 1165 (m), 1118 (m), 1103 (m), 1071 (w), 1042 (w), 1020 (w) cm^{-1}; UV (ethanol) λ_{max} 332, 296, 206 nm; MS *m/e* (relative intensity) 558 (M^+, 3), 381 (100), 321 (50), 208 (15), 207 (18); HRMS calcd for $C_{28}H_{30}N_2O_4Se$ M + 1^+ 539.14490, found 539.1449.

(±)-20-*epi*-Echitamidine Acetate (22b). A solution of (phenylselenyl)epiechitamidine **23** (7 mg, 0.013 mmol) in 20 mL of dry toluene and tributyltin hydride (17 μL, 0.065 mmol) were heated in a 120 °C oil bath. AIBN (15 μL of a 1 M solution in toluene) was added to this solution every 30 min over a 4 h period. The reaction mixture was cooled to room temperature. Concentration on a rotary evaporator, followed by flash chromatography on silica gel, eluting with ethyl acetate/ethanol/triethylamine (48:2:1), gave 4 mg (83%) of **22b**: TLC (SiO_2, ethyl acetate/ethanol/triethylamine = 48:2:1) R_f = 0.21 (CAS, dark blue); 500-MHz ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1 H), 7.18 (d, 1 H, J = 7.3 Hz), 7.14 (t, 1 H, J = 7.6 Hz), 6.89 (t, 1 H, J = 7.5 Hz), 6.81 (d, 1 H, J = 7.6 Hz), 4.96–4.93 (m, 1 H), 4.03 (bs, 1 H), 3.77 (s, 3 H), 3.18–3.15 (m, 1 H),

3.04 (dd, 1 H, J = 11.3, 14.2 Hz), 2.99–2.96 (m, 1 H), 2.85 (bs, 1 H), 2.73 (dd, 1 H, J = 5.9, 14.2 Hz), 2.30–2.27 (m, 1 H), 2.20 (dt, 1 H, J = 3.3, 13.4 Hz), 2.05 (s, 3 H), 2.01–1.96 (m, 2 H), 1.29 (d, 3 H, J = 6.3 Hz), 1.14 (dt, 1 H, J = 2.7, 13.4 Hz); 125-MHz ^{13}C NMR ($CDCl_3$) δ 170.6, 167.9 (two signals), 144.1, 135.4, 127.8, 120.9, 120.7, 109.6, 103.4, 73.7, 58.8, 58.1, 53.4, 50.9, 46.9, 45.6, 41.2, 28.6, 27.3, 21.2, 17.6; IR (film) ν_{max} 3361 (m), 2947 (m), 2929 (m), 2871 (m), 2852 (m), 1732 (s), 1673 (s), 1602 (s), 1476 (m), 1462 (s), 1433 (m), 1370 (m), 1307 (w), 1281 (m), 1241 (s), 1196 (s), 1163 (m), 1100 (m), 1058 (w), 1030 (w) cm^{-1}; UV (ethanol) λ_{max} 326, 300, 226, 204 nm; MS *m/e* (relative intensity) 383 (M + 1$^+$, 13), 382 (M$^+$, 66), 225 (100), 193 (25), 180 (25), 167 (26), 121 (48), 97 (80), 83 (45); HRMS calcd for $C_{22}H_{26}N_2O_4$ M + 1$^+$ 383.1971, found 383.1971.

(±)-20-*epi*-Echitamidine (9b). 20-*epi*-Echitamidine acetate (**22b**) (9 mg, 0.02 mmol) was dissolved in 10 mL of methanol, and 1 mL of satd potassium carbonate was added. The reaction mixture was stirred for 6 h; then the methanol was evaporated and the aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL). The organic phase was dried over sodium sulfate and concentrated on a rotary evaporator. Purification by flash chromatography, eluting with ethyl acetate/ethanol/triethylamine (40:10:2), gave 6 mg (75%) of **9b** and 2 mg (22%) of starting material **22b**.

For **9b**: 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}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1 H), 7.21 (d, J = 7 Hz, 1 H), 7.15 (t, J = 8 Hz, 1 H), 6.91 (t, J = 7 Hz, 1 H), 6.83 (d, J = 8 Hz, 1 H), 4.09 (s, 1 H), 3.83 (m, 1 H), 3.80 (s, 3 H), 3.23 (ddd, J = 7, 9, 12 Hz, 1 H), 3.14 (dd, J = 11, 14 Hz, 1 H), 3.01 (ddd, J = 4, 7, 12 Hz, 1 H), 2.96 (s, br, 1 H), 2.73 (dd, J = 6, 14 Hz, 1 H), 2.41 (ddd, J = 7, 9, 13 Hz, 1 H), 2.25 (ddd, J = 3, 3, 13 Hz, 1 H), 2.16 (s, br, OH, 1 H), 2.01 (m, 2 H), 1.27 (d, J = 6, 3 H), 1.21 (ddd, J = 3, 3, 13 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.88, 167.80, 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* (relative 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).

(±)-19-Oxo-20-*epi*-19,20-dihydroakuammicine (24). To a solution of DMSO (11 μL, 0.155 mmol) in 10 mL of CH_2Cl_2, cooled to −78 °C, was added trifluoroacetic anhydride (14 μL, 0.108 mmol), and the mixture was stirred for 30 min. 20-*epi*-Echitamidine **9b** (5.3 mg, 0.0155 mmol), dissolved in 5 mL of dry CH_2Cl_2, was added via cannula, and the reaction mixture was stirred for 2 h. Triethylamine (29 μL, 0.19 mmol) was added, and the reaction was warmed to room temperature, washed with 10% sodium bicarbonate, extracted with CH_2Cl_2 (4 × 25 mL), and dried over sodium sulfate. Concentration on a rotary evaporator, followed by flash chromatography, eluting with ethyl acetate/ethanol/triethyl amine (40:10:2), gave 5 mg (96%) of ketone **24**.

For **24**: 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}; ^{1}H 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, 49.07, 47.00, 45.15, 29.25, 27.41, 26.58; MS *m/z* (relative 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).

(±)-19-Oxo-19,20-dihydroakuammicine (25). To a solution of the ketone **24** (400 mg, 1.18 mmol) in 15 mL of dry MeOH was added a freshly prepared solution of Na (41 mg, 1.8 mmol) in 1 mL of dry MeOH at 0 °C. The mixture was allowed to stir at room temperature for 3 h. The solvent was evaporated under reduced pressure, and water was added. 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_3B (98:2:1), to afford 260 mg of isomerized ketone **25** (65% yield) and 129 mg of the recovered starting material **24** (32% yield). For **25**: mp 207 °C (recrystallized from MeOH); TLC R_f = 0.32 (CH_2Cl_2/MeOH 95:5; SiO_2 plate deactivated with Et_3N, CAS blue); UV (EtOH) λ_{max} 326, 296, 210 nm; IR (KBr) ν_{max} 3350, 2942, 2920, 2870, 1701, 1673, 1597, 1471, 1462, 1435, 1275, 1228, 1210, 1192, 1160, 1147, 1102, 1093, 742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (s, 1 H), 7.15 (d, J = 7.3 Hz, 1 H), 7.12 (t, J = 7.7 Hz, 1 H), 6.89 (t, J = 7.5 Hz, 1 H), 6.80 (d, J = 7.8 Hz, 1 H), 3.85 (s, 1 H), 3.68 (s, 3 H), 3.46 (s, br, 1 H), 3.03 (m, 1 H), 2.86 (m, 2 H), 2.80 (dd, J = 4.2, 12.2 Hz, 1 H), 2.63 (dd, J = 12.2, 12.2 Hz, 1 H), 2.29 (s, 3 H), 2.12 (ddd, J = 3.2, 3.2, 12.9 Hz, 1 H), 1.83 (m, 2 H), 1.47 (ddd, J = 3.2, 3.2, 12.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.50, 172.25, 167.71, 144.28, 135.50, 127.58, 121.13, 119.65, 109.69, 96.54, 60.63, 56.84, 54.10, 50.86, 50.15, 45.70, 43.58, 31.83, 30.92, 29.23; MS *m/z* (relative intensity) 339 (8), 338 (M$^+$, 32), 295 (6), 239 (55), 224 (36), 214 (14), 209 (80), 194 (29), 180 (64), 166 (57), 154 (14), 152 (18), 139 (15), 112 (85). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 70.99; H, 6.55; N, 8.28. Found: C, 71.02; H, 6.48; N, 8.09.

(±)-Echitamidine (8). To a mixture of ketone **25** (39 mg, 0.115 mmol) in 2 mL of MeOH at 0 °C was added $NaBH_4$ (8 mg, 0.2 mmol), in several portions. The solution was allowed to stir at room temperature for 1 h. Saturated sodium bicarbonate solution was added, 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 (95:5:1), to afford 36 mg of echitamidine (92% yield): mp 136–8 °C (EtOAc/hexanes); TLC R_f = 0.45 (CH_2Cl_2/MeOH 95:5; SiO_2 plate deactivated with Et_3N, CAS blue); UV (EtOH) λ_{max} 332, 296, 208 nm; IR (KBr) ν_{max} 3349, 2942, 2926, 2870, 1651, 1588, 1559, 1455, 1433, 1230, 1150, 1095, 724 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1 H), 7.18 (d, J = 7.3 Hz, 1 H), 7.14 (t, J = 7.7 Hz, 1 H), 6.92 (t, J = 7.5 Hz, 1 H), 6.84 (d, J = 7.7 Hz, 1 H), 4.45 (s, br, OH, 1 H), 3.87 (s, 4 H), 3.32 (s, br, 1 H), 3.26 (dq, J = 6.2, 9.2 Hz, 1 H), 3.06 (ddd, J = 6.6, 6.6, 11.5 Hz, 1 H), 2.87 (m, 1 H), 2.82 (dd, J = 7.1, 11.5 Hz, 1 H), 2.02 (ddd, J = 2.9, 2.9, 12.6 Hz, 1 H), 1.92 (dd, J = 12.5, 12.5 Hz, 1 H), 1.83 (dd, J = 6.6, 13.2 Hz, 1 H), 1.74 (m, 1 H), 1.40 (ddd, J = 3.5, 3.5, 12.6 Hz, 1 H), 1.16 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.55, 168.85, 143.78, 135.77, 127.55, 121.37, 119.76, 109.57, 96.91, 68.42, 60.98, 57.32, 54.20, 51.77, 48.24, 46.01, 43.68, 31.15, 28.91, 19.78; MS *m/z* (relative intensity) 341 (6), 340 (M$^+$, 33), 295 (10), 241 (100), 226 (15), 225 (26), 214 (7), 208 (11), 194 (13), 180 (33), 167 (19), 154 (6), 139 (10). Anal. Calcd for $C_{20}H_{24}N_2O_3 \cdot 0.5H_2O$: C, 68.74; H, 7.21; N, 8.02. Found: C, 68.92; H, 7.17; N, 7.81.

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Supplementary Material Available: Copies of ^{1}H and ^{13}C NMR and mass spectra for compounds **8**, **9a**, **9b**, **10**, **11**, **14a**, **14b**, **15a**, **15b**, **16a**, **16b**, **19a**, **19b**, **20b**, **22a**, **22b**, **23**, **24**, and **25** (43 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.