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Total syntheses of crinine and related alkaloids

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Abstract—Cyclizations of a bicyclic amine via an intramolecular Heck reaction followed by an oxidation reaction generated a tetracyclic spirocyclohexadione. From this useful intermediate, different crinine alkaloids such as crinine, buphanisine, flexinine, and augustine could be synthesized. Dienol/benzene or dienone/phenol rearrangement of this tetracyclic spirodienone afforded apogalanthamine analogs.

1. Introduction

The 2,3,4,4a-tetrahydro-1H,6H-5,10b-ethanophenanthridine (*cis*-3a-aryloctahydroindole nucleus) skeleton characterizes the crinine alkaloids such as crinine **1**, buphanisine **2**, flexinine **3**, and augustine **4**, which represent an important sub-class within the large family of *Amaryllidaceae* alkaloids (Fig. 1).[1] Many members of this sub-class display interesting biological properties including immuno-stimulatory,[2] cytotoxic,[3] antimalarial,[4] and anticholinergic activities.[5]

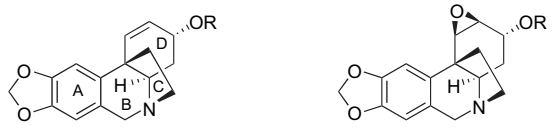

Figure 1. Structures of *Amaryllidaceae* alkaloids.

Several approaches have been developed to synthesize this skeleton, which includes a quaternary carbon. The incorporation of this sterically congested quaternary center is the critical element in the total synthesis of crinine-type alkaloids and numbers of synthetic efforts have emerged to solve this challenging problem.

The most common and generally useful syntheses developed thus far may be classified into four principal types based on the sequence of ring construction: AB→BD (biogenetic), A→C→B→D, A→C→D→B, A→D→C→B.[1,6] In the biosynthetic approach, amino spirodienones are the key intermediates, and an internal Michael cyclization serves as the main step for the construction of the skeleton by simultaneous creation of the B and D rings. The approach involving the sequence A→C→B→D requires the construction of an angular substituted phenanthridine, and the elaboration of the pyrrolidine D ring is achieved by the formation of a carbon/nitrogen bond via alkylation.

The key intermediates in the A→C→D→B and A→D→C→B approaches are 3a-arylhydroxyindoles and the formation of the B ring is generally achieved by using a Pictet–Spengler reaction.

The biomimetic approach is based on an intramolecular oxidative phenolic coupling of norbelladine analogs using vanadium oxyfluoride,[7] vanadium oxytrichloride,[8] thallium(III) trifluoroacetate,[9] anodic oxidation,[10] hypervalent iodine reagent (PIFA)[11] or on photolysis of bromophenolic compounds.[12]

An alternate synthetic route could in principle be based on intramolecular Heck cyclization.[6b,13] Our approach derives from a general program underway in the laboratory by which application of the Heck reaction followed by an oxidative step to produce spiro tricyclic dienones.[14,15] The intramolecular Heck reaction leading to 7-*exo*-trigonal cyclization has not often been described and ipso facto has rarely been used for the creation of a spiro quaternary center.

2. Results and discussions

Our synthesis started from the known aldehyde **5**[16] and amine **6**.[17] Reductive amination of these two components followed by functional transformation of the enol ether gave the amine **8**. Subsequent protection of the amine function with di-*tert*-butyl dicarbonate furnished compound **9** (75%), the precursor for the intramolecular Heck reaction

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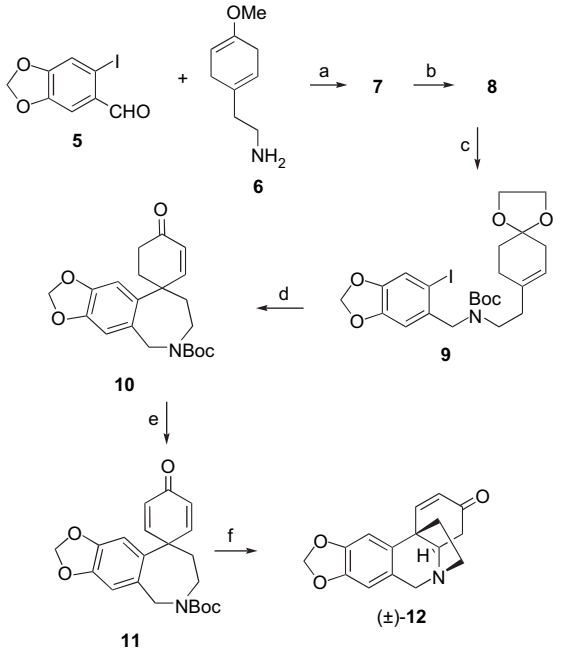
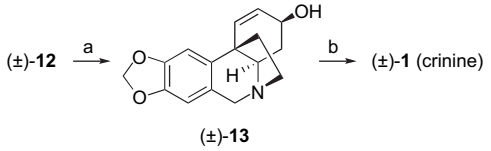
(Scheme 1). The key carbon bond-forming reaction was achieved by heating **9**, catalytic amounts of 10% [$Pd_2(dba)_3$], 20% dppe, and thallium acetate (1.2 equiv) in acetonitrile. After removal of the dioxolane group with hydrochloric acid to give **10** (56% for both steps), oxidation of the α,β-unsaturated ketone function of the latter to the corresponding dienone **11** was accomplished in 79% yield by using selenium dioxide and acetic acid in *t*-BuOH. Removal of the *N*-Boc group of **11** with trifluoroacetic acid resulted in spontaneous Michael addition to afford oxocrinine **12** (65%) (Scheme 1). A direct diastereoselective reduction of **12** to crinine **1** was not possible. However, enone **12** was stereoselectively reduced with the Luche reagent[18] to give epicrinine **13** (94%). Finally, Mitsunobu inversion of the C-3 hydroxyl provided (±)-crinine **1** (63%), which had spectral data in accordance with published values (Scheme 2).[19]

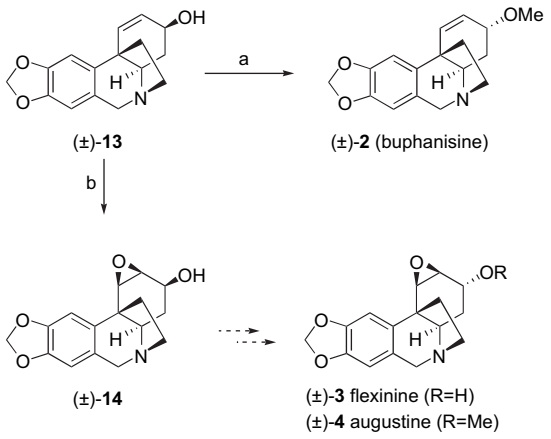


Scheme 1. Synthetic route of oxocrinine **12**: (a) MeOH, Δ, 1 h then $NaBH_4$, MeOH, AcOH, 0 °C–rt (100%); (b) $(CH_2OH)_2$, $BF_3{\cdot}Et_2O$, THF, rt (93%); (c) Boc_2O, NaOH, *t*-BuOH/H_2O, rt (75%); (d) (i) $Pd_2(dba)_3$, dppe, TIOAc, MeCN, D, 3 days; (ii) 1 N HCl, THF, rt (56%); (e) SeO_2, AcOH, *t*-BuOH, Δ, 27 h (79%); (f) TFA, CH_2Cl_2, rt then NaOH, MeOH, rt (65%).



Scheme 2. Synthetic route of (±)-crinine **1**: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, rt (94%); (b) DEAD, PPh_3, HCO_2H, THF, 3 days then 2 N NaOH, THF, rt (63%).

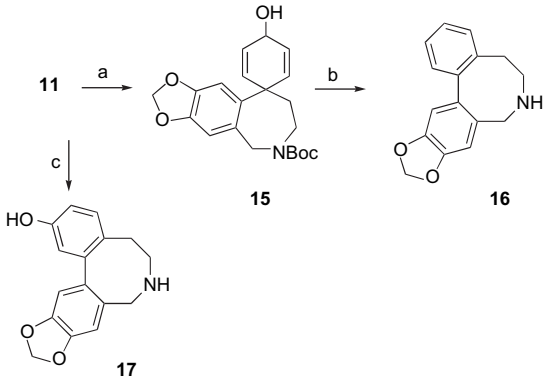
We next attempted to synthesize (±)-buphanisine **2**, which has been previously prepared via an A→C→D→B, sequence.[20] It should be noted that diastereoselective reduction of an enone function (precursor of the allylic methoxy) present in the *N*-benzyl indolone is not possible.[19] Buphanisine **2** was thus prepared by methanolysis of the allylic mesylate of (±)-epicrinine **13** with concomitant inversion of stereochemistry in 41% yield (Scheme 3).



Scheme 3. Synthetic route of buphanisine **2**, flexinine **3**, and augustine **4**: (a) (i) MsCl, NEt_3, CH_2Cl_2, rt; (ii) MeOH, rt, 40 h (41%); (b) CCl_3CN, H_2O_2 (3 equiv), TFA/CH_2Cl_2 (1/5), 24 h (42%).

Compound **12** also proved to be a valuable precursor for the synthesis of flexinine **3** and augustine **4**. These alkaloids have never been synthesized but have been isolated from different plants.[21,22] The antimalarial activities of (−)-augustine **4** in both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* are probably due to the presence of the epoxide functionality. Epoxidation of epicrinine **13** was performed with peroxymidic acid in the presence of trifluoroacetic acid to avoid oxidation of the nitrogen atom. The epoxide **14** was obtained only as the expected isomer (42%).

Finally, the synthesis of apogalanthamine analogs from spirodienone **11** via dienol/benzene[23] or dienone/phenol[24] rearrangement was examined. Reduction of **11** affords dienol **15**, which undergoes acid-catalyzed rearrangement to **16**.[25] In the same way, the dienone **11** was treated with HCl to convert it to the new biaryl **17** by dienone/phenol rearrangement (Scheme 4).



Scheme 4. Synthetic route of apogalanthamine analogs **16** and **17**: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 2 h, rt (68%); (b) concd HCl, MeCN, 95 °C, 24 h (65%); (c) concd HCl, MeCN, 1.5 h, rt (73%).

3. Conclusion

In summary, an intramolecular Heck reaction followed by a dehydrogenation reaction provided the key intermediate spirocyclohexanone **11** and an efficient strategy for the

construction of numerous alkaloids in the crinine and apogalanthamine series. An asymmetric route to these alkaloids from the valuable prochiral dienone intermediate **11** is in progress.

4. Experimental

4.1. General

NMR spectra were determined on Brucker Avance-300 with tetramethylsilane as internal reference. HMRS mass spectra were obtained on a MALDI-TOF spectrometer. Infrared (IR) spectra were recorded on a Fourier Perkin–Elmer Spectrum BX FT-IR. Elemental analyses were performed by the 'Service de microanalyses' (ICSN, CNRS, Gif-sur-Yvette).

4.2. Materials

THF was distilled from sodium/benzophenone, CH_3CN from CaH_2, MeOH from Mg/I_2, CH_2Cl_2 from P_2O_5, and NEt_3 from KOH. All separations were carried out under flash chromatographic conditions on Merck silica gel 60 (70–230 mesh) at medium pressure (200 mbar). TLC was done on Merck silica gel plates (60 F_{254}) with a fluorescent indicator.

4.2.1. [2-Iodo-4,5-methylenedioxybenzyl]-[2-(4-methoxycyclohexa-1,4-dienyl)-ethyl]amine (7). A solution of **5** (1.45 g, 5.25 mmol) and amine **6** (813.5 mg, 5.32 mmol) in dry MeOH (80 ml) was refluxed for 1 h. The solution was cooled at room temperature, then $NaBH_4$ (397 mg, 10.5 mmol, 2 equiv) was added and the pH was adjusted to 4–5 using acetic acid. The reaction mixture was stirred at room temperature for 30 min. The solvent was removed in vacuo. The residue was diluted with AcOEt and washed with saturated aqueous Na_2CO_3. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. Compound **7** (2.34 g, 100%) was isolated as a yellow oil. HRMS (ESI, *m/z*) calcd for $C_{17}H_{21}NIO_3$ (MH^+): 414.0553, found: 414.0542. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.23 (1H, s), 6.91 (1H, s), 5.95 (2H, s), 5.46 (1H, s), 4.61 (1H, s), 3.78 (2H, s), 3.72 (3H, s), 2.71 (6H, m), 2.22 (2H, t, J=6.8). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 153.0, 148.5, 147.5, 135.8, 133.1, 119.3, 118.6, 110.0, 101.6, 90.4, 87.1, 58.1, 53.9, 46.6, 37.0, 29.2. IR ($CHCl_3$) ν (cm^{-1}): 2962, 2831, 1697, 1664, 1504, 1261, 1234, 1099, 1040, 1015.

4.2.2. [2-(1,4-Dioxa-spiro[4,5]dec-7-en-8-yl)-ethyl]-[2-iodo-4,5-methylenedioxybenzyl]amine (8). To a solution of **7** (2.28 g, 5.53 mmol) in dry THF (160 ml) were added at 0 °C ethylene glycol (0.62 ml, 0.11 mmol, 2 equiv) and $BF_3\cdot OEt_2$ (0.72 ml, 5.53 mmol, 1 equiv). After being stirred for 12 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and evaporated. Compound **8** (2.33 g, 93%) was isolated as a yellow oil. HRMS (ESI, *m/z*) calcd for $C_{20}H_{23}NIO_4$ (MH^+): 444.0671, found: 444.0672. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.23 (1H, s), 6.91 (1H, s), 5.95 (2H, s), 5.30 (1H, s), 3.98 (4H, s), 3.72 (2H, s), 2.69 (2H, t, J=6.6), 2.26–2.14 (6H, m), 1.76 (2H, t, J=6.6). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 148.5, 147.5, 135.8, 135.1, 120.1, 118.6, 110.0, 108.0, 101.6, 87.0, 64.4, 58.0, 46.6, 37.3, 35.7, 31.2, 27.4. IR ($CHCl_3$) ν (cm^{-1}): 2958, 2927, 1503, 1476, 1261, 1234, 1102, 1040.

4.2.3. [2-(1,4-Dioxa-spiro[4,5]dec-7-en-8-yl)-ethyl]-[2-iodo-4,5-methylenedioxybenzyl]carbamic acid *tert*-butyl ester (9). To a solution of **8** (2.15 g, 4.86 mmol) in 1/1 mixture of *t*-BuOH/H_2O (260 ml) were added Boc_2O (1.27 g, 5.84 mmol, 1.2 equiv) and 1 N aqueous NaOH (6.8 ml, 1.4 equiv). After being stirred at room temperature for 4 h, the solvents were evaporated. The residue was extracted with AcOEt. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (elution with heptane/AcOEt 90/10, 80/20, 70/30) to give **9** (1.98 g, 75%) (rotamers) as a pale yellow oil. HRMS (ESI, *m/z*) calcd for $C_{23}H_{30}NIO_6Na$ (MNa^+): 566.1004, found: 566.1016. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.22 (1H, s), 6.72 (1H, m), 5.95 (2H, s), 5.30 (1H, s, $H_{7'}$), 4.39 and 4.32 (2H, s), 3.93 (4H, s), 3.29 and 3.19 (2H, m), 2.23–2.20 (6H, m), 1.78–1.72 (2H, m), 1.54 and 1.43 (9H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.8, 155.3, 148.8, 147.6, 134.7, 133.8, 120.6, 120.4, 118.5, 108.2, 107.9, 107.7, 101.6, 86.0, 79.9, 64.4, 55.3, 54.7, 46.0, 45.4, 35.9, 35.2, 35.7, 31.2, 28.4, 27.5. IR ($CHCl_3$) ν (cm^{-1}): 2957, 1685, 1503, 1477, 1234, 1157, 1107, 1040.

4.2.4. *tert*-Butyl-7,8-(methylenedioxy)-4′-oxo-2,3,4,5-tetrahydro-1H-[2]-benzazepine-5-spiro-1′-cyclohexa-2′-ene-2-carboxylate (10). A mixture of $Pd_2(dba)_3$ (218.5 mg, 0.24 mmol, 0.1 equiv) and dppe (190.1 mg, 0.48 mmol, 0.2 equiv) in dry CH_3CN (30 ml) was stirred at room temperature for 1 h. Then TlOAc (753.6 mg, 2.86 mmol, 1.2 equiv) and **9** (1.29 g, 2.38 mmol) in CH_3CN (50 ml) were added. After being stirred at 90 °C for 72 h, the reaction mixture was filtered through Celite (elution with AcOEt) and evaporated. The residue was dissolved in THF (60 ml), then 1 N aqueous HCl (32 ml) was added. After being stirred at room temperature for 12 h, the solvent was evaporated and the residue was extracted with AcOEt. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue (elution with heptane/AcOEt 90/10, 80/20, 70/30) afforded **10** (494.3 mg, 56%) (rotamers) as a pale yellow solid. HRMS (ESI, *m/z*) calcd for $C_{21}H_{25}NO_5Na$ (MNa^+): 394.1602, found: 371.4269. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.79 (1H, d, J=10.4), 6.72 (1H, s), 6.64 (1H, s), 6.09 (1H, d, J=10.2), 5.93 (2H), 4.48, 4.41 (2H, s), 3.74 (2H, m), 2.42–2.17 (3H, m), 1.92 (1H, m), 1.43, 1.37 (9H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 199.1, 157.7, 154.9, 154.6, 146.8, 146.1, 145.9, 135.9, 135.4, 132.0, 131.7, 127.3, 111.0, 110.5, 109.7, 101.3, 80.0, 50.4, 49.7, 44.7, 44.0, 43.5, 36.4, 35.9, 34.1, 33.3, 33.0, 28.4. IR ($CHCl_3$) ν (cm^{-1}): 2961, 2930, 1682, 1506, 1488, 1261, 1162, 1041.

4.2.5. *tert*-Butyl-7,8-(methylenedioxy)-4′-oxo-2,3,4,5-tetrahydro-1H-[2]-benzazepine-5-spiro-1′-cyclohexa-2′,5′-diene-2-carboxylate (11). A mixture of α,β-unsaturated ketone **10** (1.03 g, 2.78 mmol), SeO_2 (1.24 g, 11.1 mmol, 4 equiv), acetic acid (5.6 ml) in *t*-BuOH (76 ml) was heated at reflux for 27 h. After cooling at room temperature, the

reaction mixture was filtered through Celite (elution with AcOEt) and extracted with AcOEt. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue (elution with heptane/AcOEt 90/10, 80/20, 70/30) yielded **11** (806.8 mg, 79%) (rotamers) as a yellow solid. HRMS (ESI, *m/z*) calcd for $C_{21}H_{23}NO_5Na$ (MNa^+): 392.1471, found: 392.1474. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.97 (2H, d, J=10.1), 6.74, 6.62 (1H, s), 6.54 (1H, s), 6.28 (2H, d, J=10.1), 5.94 (2H), 4.57, 4.48 (2H, s), 3.73 (2H, m), 2.27 (2H, t, J=6.1), 1.47 and 1.39 (9H, s). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 185.6, 155.0, 154.7, 153.8, 147.0, 146.9, 132.7, 132.3, 129.3, 126.8, 110.5, 110.0, 109.6, 101.5, 80.4, 80.2, 48.9, 48.6, 47.8, 44.5, 43.6, 35.8, 35.5, 28.5, 28.4. IR ($CHCl_3$) ν (cm^{-1}): 2981, 2930, 1686 (C═O), 1665 (C═O), 1624 (C═C), 1487, 1234, 1040.

4.2.6. (±)-Oxocrinine (12). To a solution of **11** (602.3 mg, 1.63 mmol) in CH_2Cl_2 (45 ml) was added trifluoroacetic acid (14 ml). After 30 min at room temperature, the mixture was basified with solid NaOH and dissolved in aqueous MeOH. After 1 h, the solvents were evaporated and the residue was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography (elution with CH_2Cl_2/MeOH 95/5) yielded **12** (286.3 mg, 65%) as white powder. HRMS (ESI, *m/z*) calcd for $C_{16}H_{16}NO_3$ (MH^+): 270.1133, found: 270.1130. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.61 (1H, d), 6.9 (1H, s), 6.51 (1H, s), 6.08 (1H, d, J=10.4), 5.91 (2H, ABq), 4.39 (1H, d, J=16.9), 3.79 (1H, d, J=16.9), 3.63 (1H, dd, J_1=5.6, J_2=13.0), 3.53 (1H, ddd, J_1=3.8, J_2=10.4, J_3=13.7), 3.00 (1H, ddd, J_1=6.2, J_2=8.8, J_3=13.3), 2.68 (1H, dd, J_1=5.6, J_2=16.8), 2.46 (1H, dd, J_1=13.0, J_2=16.8), 2.36 (1H, ddd, J_1=3.8, J_2=8.8, J_3=12.8), 2.16 (1H, ddd, J_1=6.2, J_2=10.4, J_3=12.8). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 198.2, 149.5, 146.6, 146.4, 136.0, 128.8, 126.4, 107.3, 102.5, 101.0, 68.9, 61.9, 54.1, 44.8, 44.7, 40.2. IR ($CHCl_3$) ν (cm^{-1}): 2929, 2890, 1682, 1505, 1484, 1248, 1234, 1042.

4.2.7. (±)-Epicrinine (13). To a solution of (±)-oxocrinine **12** (50.5 mg, 0.188 mmol) in dry MeOH (5 ml) were added $NaBH_4$ (14.9 mg, 0.394 mmol, 2.1 equiv) and $CeCl_3 \cdot 7H_2O$ (146.9 mg, 0.394 mmol, 2.1 equiv). After 1 h at room temperature, the mixture was filtered through Celite (elution with MeOH) and evaporated. The residue was dissolved in CH_2Cl_2, washed twice with saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The combined organic layers were dried ($MgSO_4$) and evaporated. (±)-Epicrinine **13** (48.1 mg, 94%) was isolated as a white powder. HRMS (ESI, *m/z*) calcd for $C_{16}H_{18}NO_3$ (MH^+): 272.1282, found: 272.1287. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.77 (1H, s), 6.44 (1H, s), 6.36 (1H, dd, J_1=2.3, J_2=10.2), 5.77 (2H, s), 5.66 (1H, d, J=10.4), 4.26 (1H, d, J=16.8), 3.71 (1H, m), 3.31 (1H, ddd, J_1=4.7, J_2=10.4, J_3=14.3), 3.17 (1H, dd, J_1=3.8, J_2=13.4), 2.87 (1H, ddd, J_1=6.4, J_2=8.5, J_3=14.7), 2.13–1.94 (3H, m), 1.51 (1H, ddd, J_1=10.7, J_2=11.9, J_3=13.2). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 147.9, 147.4, 139.6, 132.8, 129.3, 126.3, 107.9, 103.9, 102.1, 68.1, 62.6, 53.7, 46–50, 45.8, 35.1. IR ($CHCl_3$) ν (cm^{-1}): 3603, 2956, 2856, 1504, 1483, 1250, 1236, 1041.

4.2.8. (±)-Crinine (1). To a solution of **13** (40.2 mg, 0.148 mmol) in dry THF (1.5 ml) were added PPh_3 (78.0 mg, 0.297 mmol, 2 equiv), distilled formic acid (25 µl, 0.663 mmol, 4.5 equiv), and DEAD (55 µl, 0.302 mmol, 2 equiv). The reaction was allowed to proceed under argon at room temperature for 3 days, while adding every 24 h extra portions of PPh_3 (78.0 mg), formic acid (25 µl), and DEAD (55 µl). The reaction mixture was then evaporated. Flash chromatography (elution with CH_2Cl_2/MeOH 97/3, 92/8, 90/10) yielded 3-*O*-formyl epicrinine (11.4 mg, 26%) as a white powder, a mixture (5.9 mg, 3-*O*-formyl epicrinine/3-*O*-formyl-crinine 35/65), and 3-*O*-formyl-crinine (28.9 mg, 65%) as a white powder. To a solution of 3-*O*-formyl-crinine (28.9 mg, 0.097 mmol) in THF (3 ml) was added 2 N aqueous NaOH (2.2 ml). After 1.5 h at room temperature, the solvent was evaporated. The residue was dissolved in $CHCl_3$, washed with 33% aqueous NH_3, and extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. (±)-Crinine **1** (25.3 mg, 97%) was yielded as a white powder. HRMS (ESI, *m/z*) calcd for $C_{16}H_{18}NO_3$ (MH^+): 272.1287, found: 272.1287. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.78 (1H, s), 6.59 (1H, d, J=9.8), 6.42 (1H, s), 5.97 (1H, dd, J_1=5.1, J_2=9.8), 5.83 (2H, ABq), 4.42 (1H, d, J=16.8), 4.36 (1H, m), 3.75 (1H, d, J=16.8), 3.39–3.27 (2H, m), 2.85 (1H, ddd, J_1=5.9, J_2=8.9, J_3=13.9), 2.19 (1H, ddd, J_1=4.2, J_2=9.0, J_3=12.7), 1.97–1.88 (2H, m), 1.75 (1H, ddd, J_1=4.2, J_2=J_3=13.6). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 146.2, 145.8, 138.2, 132.3, 127.5, 126.2, 107.0, 102.9, 100.8, 64.2, 62.9, 62.1, 53.6, 44.3, 44.2, 32.8. IR ($CHCl_3$) ν (cm^{-1}): 3690, 3343, 2853, 1602, 1504, 1262, 1004, 938.

4.2.9. (±)-Buphanisine (2). To a solution of **13** (45.1 mg, 0.17 mmol) in dry CH_2Cl_2 (4.4 ml) were added Et_3N (60 µl, 0.43 mmol, 2.5 equiv) and MsCl (33 µl, 0.43 mmol, 2.5 equiv). After 2 h at room temperature, the solvent was evaporated, and the residue was dissolved in dry MeOH (5 ml). After 40 h at room temperature, the solvent was evaporated, the residue was dissolved in $CHCl_3$, washed with saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Preparative thin-layer chromatography (elution with CH_2Cl_2/MeOH 9/1) yielded (±)-buphanisine **2** (19.6 mg, 41%) as a white powder. HRMS (ESI, *m/z*) calcd for $C_{17}H_{20}NO_3$ (MH^+): 286.1438; found: 286.1443. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.81 (1H, s), 6.59 (1H, d, J=10.0), 6.45 (1H, s), 5.94 (1H, ddd, J_1=1.0, J_2=5.1, J_3=10.0), 5.86 (2H, d, J=1.3), 4.38 (1H, d, J=16.9), 3.81 (1H, m), 3.75 (1H, d, J=16.9), 3.34 (3H, s), 3.39–3.29 (2H, m), 2.87 (1H, ddd, J_1=5.8, J_2=9.2, J_3=12.8), 2.19–2.03 (2H, m), 1.89 (1H, ddd, J_1=5.8, J_2=10.6, J_3=12.0), 1.58 (1H, ddd, J_1=4.0, J_2=J_3=13.6). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 146.0, 145.6, 138.5, 133.0, 126.4, 125.3, 106.9, 102.9, 100.7, 72.7, 63.0, 62.4, 56.4, 53.6, 44.3, 28.9. IR ($CHCl_3$) ν (cm^{-1}): 2962, 2930, 1602, 1505, 1261, 1092, 1041, 1014.

4.2.10. (±)-1β,2β-Epoxy-epicrinine (14). A solution of CCl_3CN (26 µl, 0.26 mmol, 3 equiv) and 30% aqueous H_2O_2 (30 µl, 0.26 mmol, 3 equiv) in dry CH_2Cl_2 (0.5 ml) was stirred at room temperature for 1.5 h. Then, the solution

was transferred via syringe to a flask containing **13** (23.5 mg, 0.09 mmol, 1 equiv) in a mixture of CH_2Cl_2/TFA (1.1 ml/0.3 ml). After 24 h at room temperature, the reaction mixture was basified with 33% aqueous NH_3 (pH 10) and extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Preparative thin-layer chromatography (elution with CH_2Cl_2/MeOH 9/1) yielded **14** (10.4 mg, 42%) as a white powder. HRMS (ESI, *m/z*) calcd for $C_{16}H_{17}NO_4$ (MH^+): 288.1236; found: 288.1225. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.89 (1H, s), 6.49 (1H, s), 5.91 (2H, s), 4.38 (1H, d, J=16.9), 4.14 (1H, ddd, J_1=10.6, J_2=5.4, J_3=1.6), 3.84 (1H, d, J=3.8), 3.72 (1H, d, J=16.9), 3.46 (1H, d, J=3.8), 3.30 (1H, ddd, J_1=4.5, J_2=10.9, J_3=15.3), 2.91 (1H, dd, J_1=3.1, J_2=13.3), 2.84 (1H, ddd, J_1=5.8, J_2=9.2, J_3=13.0), 2.48 (1H, ddd, J_1=5.8, J_2=10.9, J_3=13.4), 2.0 (1H, ddd, J_1=4.7, J_2=9.2, J_3=13.4), 1.84 (1H, ddd, J_1=3.4, J_2=4.5, J_3=12.1), 1.39 (1H, ddd, J_1=10.9, J_2=J_3=12.1). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 146.5, 146.1, 137.1, 126.0, 107.2, 102.7, 101.0, 68.2, 67.5, 62.0, 58.5, 55.1, 52.5, 41.4, 38.7, 30.5. IR ($CHCl_3$) ν (cm^{-1}): 3690, 2926, 1505, 1483, 1314, 1262, 1002, 938.

4.2.11. *tert*-Butyl-7,8-(methylenedioxy)-4′-hydroxy-2,3,4,5-tetrahydro-1H-[2]-benzazepine-5-spiro-1′-cyclohexa-2′,5′-diene-2-carboxylate (15). To a solution of **11** (104.4 mg, 0.283 mmol) in dry MeOH (7 ml) were added $CeCl_3 \cdot 7H_2O$ (221.3 mg, 0.594 mmol, 2.1 equiv) and $NaBH_4$ (22.5 mg, 0.595 mmol, 2.1 equiv). After 1 h at room temperature, the mixture was filtered though Celite (elution with MeOH) and evaporated. The residue was diluted with $CHCl_3$, washed with 33% aqueous NH_3, and extracted with $CHCl_3$. The combined organic layers were washed saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Preparative thin-layer chromatography (elution: heptane/AcOEt 1/1) yielded a 1/1 separable diastereoisomeric mixture **15** (74.0 mg, 71%) (rotamers) as a white solid. HRMS (ESI, *m/z*) calcd for $C_{21}H_{28}NO_5Na$ (MNa^+): 394.1626; found: 394.1630. IR ($CHCl_3$) ν (cm^{-1}): 3691, 3586, 2959, 1684, 1602, 1505, 1416, 1261, 1099 (C–O), 1011 (C–O). Fraction 1: **15a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.60, 6.57 (1H, s), 6.65, 6.53 (1H, s), 5.9–5.86 (6H, m), 4.61 (1H, m), 4.47, 4.39 (2H, s), 3.63 (2H, m), 2.09 (2H, m), 1.42, 1.34 (9H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.1, 146.7, 145.6, 136.1, 135.8, 135.7, 135.3, 131.5, 131.2, 125.3, 125.1, 110.9, 110.6, 109.9, 109.5, 101.2, 79.8, 62.2, 49.0, 48.1, 45.1, 43.8, 43.5, 37.9, 37.8, 28.5, 28.4. Fraction 2: **15b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.74, 6.70 (1H, s), 6.67, 6.55 (1H, s), 5.9–5.87 (6H, m), 4.54 (1H, m), 4.49, 4.40 (2H, s), 3.63 (2H, m), 2.04 (2H, m), 1.44, 1.36 (9H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 155.0, 146.5, 145.6, 135.6, 131.5, 131.1, 125.4, 111.1, 110.7, 109.9, 109.4, 101.2, 79.8, 61.7, 49.0, 48.1, 45.4, 43.3, 42.5, 38.2, 38.0, 28.5, 28.4.

4.2.12. 2,3-Methylenedioxy-5,6,7,8-tetrahydrodibenzo[*c*,*e*]-azocine (16). To a solution of **15** (37.3 mg, 0.10 mmol) in dry CH_3CN (5 ml) was added 35% aqueous HCl. After 1.5 h at room temperature, the reaction mixture was basified with 33% aqueous NH_3 (pH 10) and extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Preparative thin-layer chromatography (elution: CH_2Cl_2/MeOH 9/1) afforded **16** (18.6 mg, 73%) as a white solid. HRMS (ESI, *m/z*) calcd for $C_{16}H_{16}NO_2$ (MH^+): 254.1187; found: 254.1183. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.37–7.22 (4H, m), 6.88 (1H, s), 6.80 (1H, s), 6.00 (2H, ABq, J=1.0), 3.87 (1H, d, J=13.9), 3.42 (1H, dd, J_1=6.8, J_2=13.9), 3.11 (1H, d, J=13.9), 2.86–2.78 (2H, m), 2.41 (1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 147.6, 146.7, 140.7, 139.9, 133.4, 133.1, 129.4, 129.3, 128.1, 126.1, 109.5, 109.4, 101.2, 50.2, 49.0, 36.3. IR ($CHCl_3$) ν (cm^{-1}): 3064, 2928, 1702, 1675 (Ar), 1601 (Ar), 1504, 1262, 1011.

4.2.13. 2,3-Methylenedioxy-5,6,7,8-tetrahydrodibenzo-[*c*,*e*]-azocin-11-ol (17). To a solution of **11** (50.5 mg, 0.188 mmol) in dry CH_3CN (7 ml) was added 35% aqueous HCl (4.6 ml) at room temperature. After 24 h at 95 °C, the reaction mixture was cooled at room temperature, basified with 33% aqueous NH_3 (pH 10), and extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Flash chromatography (alumina, elution: CH_2Cl_2, CH_2Cl_2/MeOH 97.5/2.5, 96/4, 90/10) afforded **17** (49.9 mg, 62%) as a white powder. HRMS (ESI, *m/z*) calcd for $C_{16}H_{16}NO_3$ (MH^+): 270.1120, found: 270.1130. ^{1}H NMR (CD_3OD, 300 MHz) δ (ppm): 7.04 (1H, d, J=8.3), 6.85 (1H, s), 6.75 (1H, dd, J_1=2.6, J_2=8.3), 6.70 (1H, s), 6.63 (1H, d, J=2.6), 5.95 (2H, ABq, J=1.0), 3.73 (1H, d, J=13.8), 3.23 (1H, dd, J_1=7.0, J_2=13.8), 3.02 (1H, d, J=13.8), 2.74–2.59 (2H, m), 2.20 (1H, dd, J_1=10.0, J_2=14.0). ^{13}C NMR (CD_3OD, 75.5 MHz) δ (ppm): 156.6, 149.0, 148.3, 142.1, 135.6, 133.6, 133.2, 131.5, 116.7, 116.3, 110.7, 109.9, 101.2, 50.7, 50.2, 35.6. IR ($CHCl_3$) ν (cm^{-1}): 3691 (O–H), 3599 (O–H), 3290 (NH), 2961, 2855, 1604 (Ar), 1572 (Ar), 1503, 1261, 1040 (C–O), 1015 (C–O).

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