Intramolecular Chemoselective Acylation of a Suitably Substituted Isoindole: Synthesis of (±)-Chilenine and (±)-Deoxychilenine

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Abstract: Starting from 3,4-dimethoxyhomophthalic anhydride and 6-bromohomopiperonylamine, concise and efficient syntheses of Chilean berberis products chilenine and deoxychilenine have been demonstrated via partially divergent routes by taking advantage of facile air-oxidation of homophthalimide along with intramolecular chemoselective acylation as the key steps.

Key words: homophthalic anhydride, isoindole, chemoselective acylation, chilenine, deoxychilenine, total synthesis

Chilenine (**1**), deoxychilenine (**2**), and lennoxamine (**3**) were isolated, respectively, from *Berberis empetrifolia*, *Berberis actinacantha*, and *Berberis darwinii*[1] and they belong to the isoindolobenzazepine class of alkaloids (Figure 1).[2] These natural products are biogenetically related to protoberberines, hence their ring systems are accessible by oxidation of berberine alkaloids.[3] On the basis of the important biological properties of the berberine class of compounds and the intriguing structural features of these three natural products **1**–**3**, several elegant synthesis of chilenine and lennoxamine have been reported.[4,5] Recently, Honda and Sakamaki have also reported the first synthesis of deoxychilenine employing a novel palladium-catalyzed intramolecular arylation.[4c] In continuance of our comprehensive studies on cyclic anhydrides and derivatives to bioactive natural and unnatural products,[6] recently we serendipitously witnessed the facile air oxidation of homophthalimides and utilized it for the synthesis of nuevamine and isoindolo-β-carboline.[7] In this context, we herein report the total synthesis of chilenine and deoxychilenine from 3,4-dimethoxyhomophthalic anhydride via partially divergent routes utilizing intramolecular acylation as the decisive step[8] (Scheme 1).

The reaction of 3,4-dimethoxyhomophthalic anhydride (**4**)[9,10] and homopiperonylamine (**5a**) in refluxing *o*-dichlorobenzene furnished the required homophthalimide **6a** in 78% yield. As expected, the homophthalimide **6a** underwent facile air oxidation at an activated benzylic position and provided the prospective precursor trione **7a** in 94% yield. In principle the selective Friedel–Crafts-type intramolecular acylation of trione **7a** would provide direct access to chilenine (**1**) via a ring-expansion and recyclization mechanism. However, all attempts to transform the trione **7a** into **1** utilizing acid-catalyzed (TFA, H_2SO_4/AcOH, PTSA/xylene), Lewis acid catalyzed ($BF_3{\cdot}OEt_2$, $AlCl_3$, $AuCl_3$, TMSOTf), and thermal cyclization (DMSO reflux, neat heating 200 °C) conditions were unsuccessful and always ended up with either the unreacted starting material or excessive decomposition. The trione **7a** on base-catalyzed regioselective methanolysis provided the ring-contraction product lactamol **8a** in 96% yield with the desired free ester moiety.

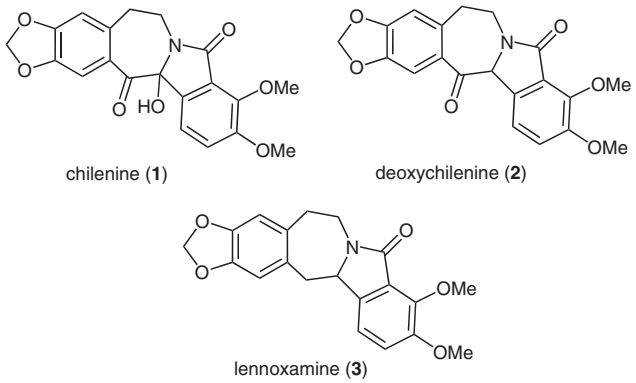

Figure 1 Chilean berberis products

As depicted in Scheme 1, the product **8a** was also directly obtained in one step from the corresponding homophthalimide **6a** in 94% yield by utilizing the combination of a similar set of reaction conditions. Conversely, the multifunctional compound **8a** under acidic conditions (TFA, H_2SO_4/AcOH, PTSA/CH_2Cl_2) was very prone to six-membered intramolecular dehydrative cyclization and, under the basic hydrolytic conditions, it had a propensity for decarboxylation. Hence all initial attempts to directly transform the trione **7a** and lactamol **8a** to chilenine (**1**) were not successful.

In the second segment of studies, starting from 3,4-dimethoxyhomophthalic anhydride (**4**) and 6-bromohomopiperonylamine (**5b**), we similarly synthesized the *o*-bromotrione **7b** and *o*-bromolactamol **8b** in 96% and 95% yields, respectively, in order to use lithium–halogen exchange to induce the essential intramolecular cyclizations. Again, the trione **7b** on treatment with *tert*-butyllithium in tetrahydrofuran at –78 °C and –100 °C, with or without hexamethylphosphoramide, underwent instantaneous complete decomposition. However, the *o*-bromolactamol **8b** on treatment with *tert*-butyllithium (2.20 equiv) in tetrahydrofuran at –78 °C underwent intramo-

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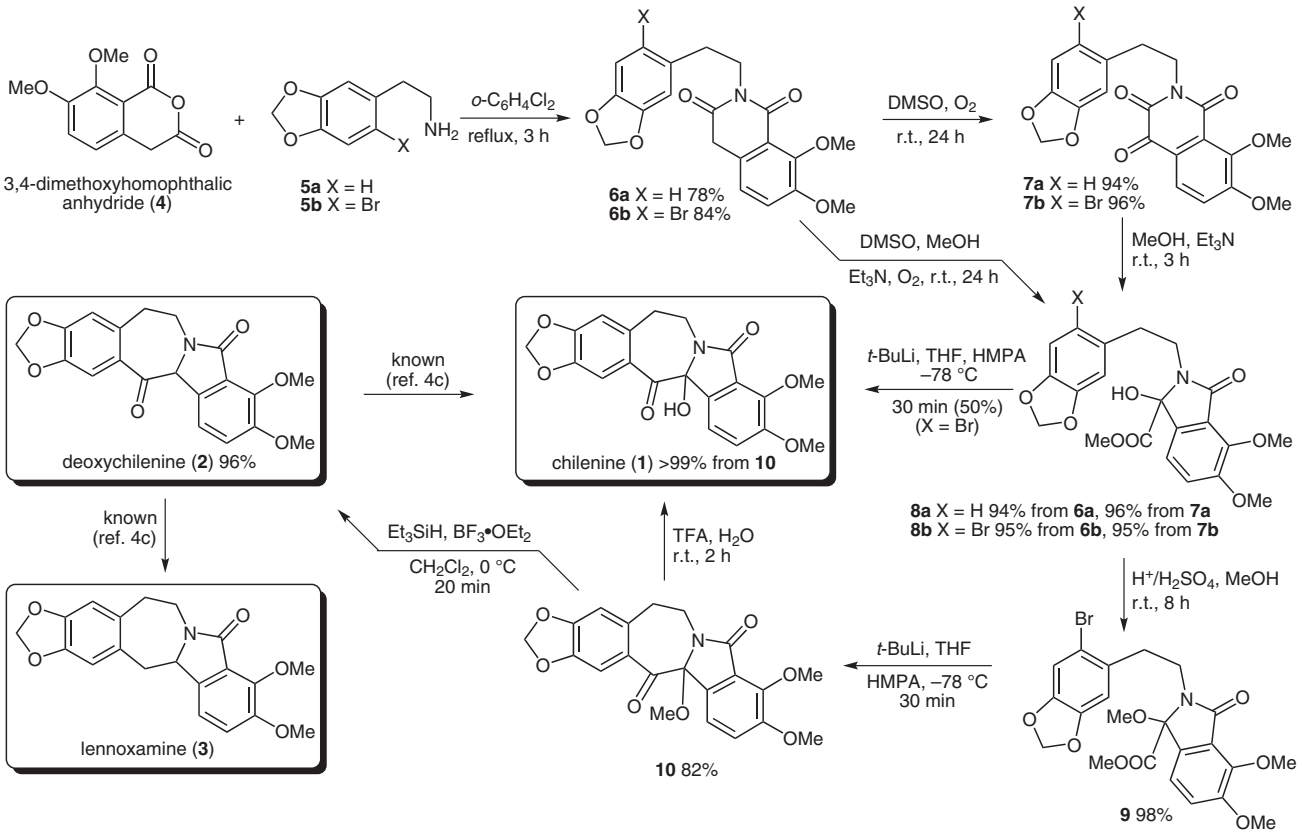

Scheme 1 Synthesis of chilenine and deoxychilenine

lecular chemoselective acylation to form the crucial seven-membered benzazepine core and furnished the target compound chilenine (**1**), but in only 15–20% yield together with a large amount of debrominated staring material (45% of **8a**).

In the above-mentioned reaction the use of hexamethylphosphoramide as a co-solvent improved the yield to 45–50%. In the conversion of **8b** into **1**, the instability of in situ generated oxyanionic species from compound **8b** and/or its display of ring-chain tautomerism might plausibly have an effect on the efficiency of the intramolecular acylation reaction. Hence the free tertiary hydroxy group in compound **8b** was transformed into methoxy by treatment with excess methanol and concentrated sulfuric acid to obtain lactamol methyl ether **9** in quantitative yield. The above-specified hypothesis turned out to be reasonable and finally treatment of **9** in tetrahydrofuran and hexamethylphosphoramide mixture with *tert*-butyllithium (1.10 equiv) induced intramolecular acylation to give the corresponding desired cyclized product **10** in 82% yield. Herein the intramolecular chemoselective demethoxylative acylation to form the seven-membered benzazepine ring system over the possible nucleophilic substitution of an angular methoxy group to furnish the corresponding six-membered piperidine unit is remarkable. The compound **10** on usual acid-catalyzed hydrolysis furnished chilenine (**1**) in quantitative yield, while the same on treatment with triethylsilane underwent Lewis acid catalyzed displacement of the angular OMe group with a hydride ion to provide deoxychilenine (**2**) in 96% yield.

In the ^{1}H NMR spectrum of deoxychilenine (**2**) the methine proton appeared as singlet at $\delta = 5.15$ ppm and it was not exchangeable with deuterium, indicating the absence of any associated keto–enol tautomerism. The analytical and spectral data obtained for both chilenine and deoxychilenine were in agreement with the reported data.[1,4f] The conversions of deoxychilenine (**2**) into chilenine (**1**) and lennoxamine (**3**) are well known in the literature.[4c]

In summary, starting with the unsymmetrical cyclic anhydride we have accomplished five steps total synthesis of berberis natural products chilenine and deoxychilenine in decent overall yields via a penultimate-stage common intermediate. In this present approach, the critical *tert*-butyllithium-induced intramolecular chemoselective acylation that delivered the benzazepine core is noteworthy.

Melting points are uncorrected. ^{1}H NMR spectra were recorded on Bruker NMR spectrometers operating at 200 and 400 MHz, respectively, with TMS as an internal standard. ^{13}C NMR spectra were recorded on the same instruments operating at 50, 100, and 125 MHz. IR spectra were recorded on a Shimadzu FT-IR spectrophotometer. Mass spectra and HRMS were taken on ESIMS mass spectrometer and HRMS (ESI), respectively. Column chromatographic separations used silica gel (60–120 mesh); petroleum ether = PE. Commercially available *t*-BuLi, $BF_3{\cdot}OEt_2$, and Et_3SiH were used.

2-[2-(1,3-Benzodioxol-5-yl)ethyl]-7,8-dimethoxyisoquinoline-1,3(2*H*,4*H*)-dione (6a); Typical Procedure

A stirred soln of 3,4-dimethoxyhomophthalic anhydride[10] (**4**, 500 mg, 2.25 mmol) and homopiperonylamine (**5a**, 371 mg, 2.25 mmol) was refluxed in *o*-dichlorobenzene (10 mL) for 3 h. The mixture was allowed to cool to r.t. and it was then loaded onto a chromatography column (silica gel, PE to remove *o*-dichlorobenzene and then PE–EtOAc, 6:4) to give pure **6a** (648 mg, 78%) as a yellow solid; mp 155–157 °C.

IR ($CHCl_3$): 1717, 1673 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.77–2.89 (m, 2 H), 3.90 (s, 3 H), 3.92 (br s, 2 H), 3.94 (s, 3 H), 4.07–4.18 (m, 2 H), 5.92 (s, 2 H), 6.74 (s, 2 H), 6.82 (s, 1 H), 6.97 (d, *J* = 8 Hz, 1 H), 7.15 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.7, 36.1, 41.6, 56.2, 61.2, 100.7, 108.0, 109.3, 117.4, 119.3, 121.7, 122.6, 126.4, 132.3, 145.9, 147.4, 150.9, 152.9, 162.5, 169.6.

MS (ESI): *m*/*z* = 392 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 64.79; H, 4.97; N, 3.67.

2-[2-(6-Bromo-1,3-benzodioxol-5-yl)ethyl]-7,8-dimethoxyisoquinoline-1,3(2*H*,4*H*)-dione (6b)

Following the typical procedure for **6a** using 3,4-dimethoxyhomophthalic anhydride (**4**, 1.00 g, 4.50 mmol) and 6-bromohomopiperonyl amine (**5b**, 1.09 g, 4.50 mmol) gave **6b** (1.69 g, 84%) as a yellow solid; mp 172–174 °C.

IR ($CHCl_3$): 1717, 1673 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.00 (dd, *J* = 10, 8 Hz, 2 H), 3.90 (s, 3 H), 3.91 (s, 2 H), 3.92 (s, 3 H), 4.18 (dd, *J* = 10, 8 Hz, 2 H), 5.94 (s, 2 H), 6.82 (s, 1 H), 6.96 (s, 1 H), 6.96 (d, *J* = 8 Hz, 1 H), 7.15 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.1, 36.3, 39.9, 56.4, 61.3, 101.6, 110.4, 112.6, 114.7, 117.6, 119.4, 122.7, 126.5, 131.4, 147.0, 147.3, 151.1, 153.0, 162.6, 169.7.

MS (ESI): *m*/*z* = 470, 472 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{19}BrNO_6$: 448.0396; found: 448.0394.

2-[2-(1,3-Benzodioxol-5-yl)ethyl]-7,8-dimethoxyisoquinoline-1,3,4(2*H*)-trione (7a); Typical Procedure

To a stirred soln of **6a** (300 mg, 0.813 mmol) in DMSO (10 mL) at r.t. was bubbled excess O_2 gas for 12 h and then it was further stirred for 12 h. To the formed yellow-colored mixture was added EtOAc (30 mL) and the organic layer was washed with brine (3 × 15 mL) to remove DMSO and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by column chromatography (silica gel, PE–EtOAc, 1:1) gave **7a** (292 mg, 94%) as a yellow solid; mp 186–188 °C.

IR ($CHCl_3$): 1681 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.85–2.92 (m, 2 H), 3.97 (s, 3 H), 4.04 (s, 3 H), 4.17–4.24 (m, 2 H), 5.93 (s, 2 H), 6.72 (s, 2 H), 6.83 (s, 1 H), 7.29 (d, *J* = 8 Hz, 1 H), 8.09 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.7, 42.5, 56.6, 61.5, 100.9, 108.3, 109.4, 116.3, 121.9, 122.6, 123.9, 126.5, 131.8, 146.2, 147.7, 151.2, 157.1, 160.0, 161.1, 173.8.

MS (ESI): *m*/*z* = 406 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{18}NO_7$: 384.1083; found: 384.1083.

2-[2-(6-Bromo-1,3-benzodioxol-5-yl)ethyl]-7,8-dimethoxyisoquinoline-1,3,4(2*H*)-trione (7b)

Following the typical procedure for **7a** using **6b** (200 mg, 0.446 mmol) gave **7b** (198 mg, 96%) as a yellow solid; mp 192–194 °C.

IR ($CHCl_3$): 1727, 1685 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.97 (t, *J* = 8 Hz, 2 H), 3.87 (s, 3 H), 3.96 (s, 3 H), 4.19 (t, *J* = 8 Hz, 2 H), 5.87 (s, 2 H), 6.75 (s, 1 H), 6.88 (s, 1 H), 7.22 (d, *J* = 8 Hz, 1 H), 8.01 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.9, 40.7, 56.6, 61.4, 101.6, 110.4, 112.6, 114.6, 116.2, 122.5, 123.9, 126.4, 130.8, 147.2, 147.4, 151.1, 157.1, 159.9, 161.0, 173.7.

MS (ESI): *m*/*z* = 484, 486 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{16}BrNO_7$ C, 51.97; H, 3.49; N, 3.03. Found: C, 52.05; H, 3.64; N, 3.32.

Methyl 2-[2-(1,3-Benzodioxol-5-yl)ethyl]-1-hydroxy-4,5-dimethoxy-3-oxo-2,3-dihydro-1*H*-isoindole-1-carboxylate (8a); Typical Procedures

Method A: To the soln of **6a** (300 mg, 0.813 mmol) in a mixture of DMSO (20 mL) and MeOH (5 mL) at r.t. was added Et_3N (0.50 mL) and into the mixture was bubbled excess O_2 gas for 6 h and then it was further stirred for 18 h. To the formed dark-blue-colored mixture was added EtOAc (30 mL) and the organic layer was washed with brine (3 × 15 mL) to remove DMSO and with 2 M HCl (10 mL) and brine (15 mL), and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by column chromatography (silica gel, PE–EtOAc, 4:6) gave **8a** (317 mg, 94%) as a brown solid.

Method B: To a stirred soln of **7a** (200 mg, 0.522 mmol) in MeOH (5 mL) was added Et_3N (cat., 1 drop) at r.t. and the mixture was stirred for 3 h. Concentration of the organic layer in vacuo followed by column chromatography (silica gel, PE–EtAOc, 4:6) furnished **8a** (208 mg, 96%) as a brown solid; mp 138–140 °C.

IR ($CHCl_3$): 3501, 1737, 1705 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.74–3.01 (m, 2 H), 3.20–3.38 (m, 1 H), 3.61–3.79 (m, 1 H), 3.72 (s, 3 H), 3.88 (s, 3 H), 4.09 (s, 3 H), 4.65 (br s, 1 H), 5.92 (s, 2 H), 6.68–6.78 (m, 3 H), 7.04 (d, *J* = 8 Hz, 1 H), 7.12 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.3, 41.9, 53.8, 56.3, 62.3, 87.4, 100.7, 108.1, 109.1, 116.0, 117.1, 121.5, 122.8, 132.6, 136.0, 145.9, 146.5, 147.5, 154.0, 165.8, 171.1.

MS (ESI): *m*/*z* = 438 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{22}NO_8$: 416.1345; found: 416.1343.

Methyl 2-[2-(6-Bromo-1,3-benzodioxol-5-yl)ethyl]-1-hydroxy-4,5-dimethoxy-3-oxo-2,3-dihydro-1*H*-isoindole-1-carboxylate (8b)

Following the typical procedure for **8a** method A using **6b** (1.40 g, 3.12 mmol) gave **8b** (1.46 g, 95%) as a brown solid and method B using **7b** (150 mg, 0.324 mmol) gave **8b** (152 mg, 95%) a brown solid; mp 178–180 °C.

IR ($CHCl_3$): 3503, 1737, 1706 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.85–3.19 (m, 2 H), 3.23–3.41 (m, 1 H), 3.59–3.74 (m, 1 H), 3.76 (s, 3 H), 3.90 (s, 3 H), 4.12 (s, 3 H), 4.61 (br s, 1 H), 5.95 (s, 2 H), 6.84 (s, 1 H), 6.99 (s, 1 H), 7.09 (br s, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.9, 39.9, 54.2, 56.5, 62.5, 87.3, 101.6, 110.5, 112.7, 114.5, 116.1, 117.0, 123.0, 131.7, 136.0, 146.9, 147.1, 147.4, 154.3, 166.0, 171.8.

MS (ESI): *m*/*z* = 516, 518 $[M + Na]^+$.

Anal. Calcd for $C_{21}H_{20}BrNO_8$: C, 51.03; H, 4.08; N, 2.83. Found: C, 50.64; H, 3.87; N, 2.48.

Methyl 2-[2-(6-Bromo-1,3-benzodioxol-5-yl)ethyl]-1,4,5-trimethoxy-3-oxo-2,3-dihydro-1*H*-isoindole-1-carboxylate (9)

To a stirred soln of **8b** (1.00 g, 2.02 mmol) in MeOH (30 mL) was added concd H_2SO_4 (2 mL) in a dropwise fashion at 0 °C. The mixture was stirred at r.t. for 8 h and then MeOH was distilled off under the reduced pressure. The obtained residue was dissolved in EtOAc (60 mL) and the organic layer was washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL), and dried (Na_2SO_4). Concentration of organic layer in vacuo followed by column chromatography (silica gel, PE–EtOAc, 1:1) furnished **9** (1.00 g, 98%) as an off-white solid; mp 124–126 °C.

IR ($CHCl_3$): 1753, 1706 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.95 (s, 3 H), 3.00–3.22 (m, 2 H), 3.30–3.69 (m, 2 H), 3.76 (s, 3 H), 3.91 (s, 3 H), 4.13 (s, 3 H), 5.95 (s, 2 H), 6.87 (s, 1 H), 6.99 (s, 1 H), 7.09 (d, *J* = 8 Hz, 1 H), 7.19 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.1, 40.6, 50.4, 53.4, 56.5, 62.5, 92.6, 101.6, 110.5, 112.7, 114.5, 116.0, 118.0, 124.0, 131.3, 132.2, 147.1, 147.2, 147.5, 154.5, 166.6, 168.2.

MS (ESI): *m*/*z* = 530, 532 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{22}H_{22}BrNO_8$: 508.0607; found: 508.0630.

9,10,12b-Trimethoxy-5*H*-[1,3]dioxolo[4′′,5′′:4′,5′]benzo[1′,2′:4,5]azepino[2,1-*a*]isoindole-8,13(6*H*,12b*H*)-dione (10)

To a stirred soln of **9** (500 mg, 0.984 mmol) in THF and HMPA (4:1, 15 mL) was added 1.30 M *t*-BuLi (0.90 mL, 1.18 mmol) at –78 °C in a dropwise fashion. The mixture was further stirred for 30 min at the same temperature and then it was allowed to reach r.t. The reaction was quenched by adding few drops of sat. aq NH_4Cl. After removal of THF in vacuo, EtOAc (50 mL) was added to the mixture and the organic layer was washed with H_2O (20 mL) and brine (20 mL), and dried (Na_2SO_4). Concentration of organic layer in vacuo followed by column chromatography (silica gel, PE–EtOAc, 6:4) furnished **10** (0.32 g, 82%) as an off-white solid; mp 150–152 °C (Lit.[4o] 146–147 °C).

IR ($CHCl_3$): 1701, 1685 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.80–3.00 (m, 1 H), 3.06 (s, 3 H), 3.36–3.60 (m, 2 H), 3.91 (s, 3 H), 4.03 (s, 3 H), 4.14–4.40 (m, 1 H), 5.97 (s, 2 H), 6.67 (s, 1 H), 6.82 (s, 1 H), 7.13 (d, *J* = 8 Hz, 1 H), 7.51 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.5, 38.7, 51.1, 56.4, 62.3, 94.7, 101.8, 109.0, 109.2, 116.2, 120.4, 123.9, 130.5, 131.6, 133.5, 146.6, 146.9, 151.4, 154.3, 166.4, 199.4.

MS (ESI): *m*/*z* = 420 $[M + Na]^+$.

12b-Hydroxy-9,10-dimethoxy-5*H*-[1,3]dioxolo[4′′,5′′:4′,5′]benzo[1′,2′:4,5]azepino[2,1-*a*]isoindole-8,13(6*H*,12b*H*)-dione (Chilenine, 1)

Method A: To a stirred soln of **8b** (200 mg, 0.40 mmol) in THF and HMPA (4:1, 10 mL) was added 1.30 M *t*-BuLi (0.68 mL, 0.89 mmol) at –78 °C in a dropwise fashion. The mixture was further stirred for 30 min at the same temperature and then allowed to warm to r.t. The reaction was quenched by adding few drops of sat. aq NH_4Cl. After removing THF in vacuo, EtOAc (30 mL) was added to the mixture and the organic layer was further washed with H_2O (10 mL), brine (10 mL), and dried (Na_2SO_4). Concentration of organic layer in vacuo followed by column chromatography (silica gel, PE–EtOAc, 4:6) gave **1** (78 mg, 50%) as a faint yellow solid.

Method B: Compound **10** (100 mg, 0.25 mmol) was stirred in 50% aq TFA (4 mL) at r.t. for 2 h. The reaction was quenched by the addition of sat. aq $NaHCO_3$ and extracted with EtOAc (20 mL) and the organic layer was washed with brine (10 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo followed by column chromatography (silica gel, PE–EtOAc, 4:6) furnished **1** (97 mg, 100%) as a faint yellow solid; mp 115–116 °C (Lit.[4n] 114–116 °C).

IR ($CHCl_3$): 3402, 1704 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.04 (ddd, *J* = 15, 6, 4 Hz, 1 H), 3.38 (ddd, *J* = 14, 11, 6 Hz, 1 H), 3.59 (ddd, *J* = 14, 6, 4 Hz, 1 H), 3.84 (s, 3 H), 3.95 (s, 3 H), 4.18 (ddd, *J* = 14, 10, 4 Hz, 1 H), 4.56 (br s, 1 H), 5.94 (d, *J* = 2 Hz, 1 H), 5.96 (d, *J* = 2 Hz, 1 H), 6.66 (s, 1 H), 6.74 (s, 1 H), 7.01 (d, *J* = 10 Hz, 1 H), 7.40 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.0, 37.8, 56.4, 62.3, 90.4, 101.8, 108.6, 109.5, 116.3, 119.2, 122.6, 129.8, 133.7, 135.6, 146.0, 146.8, 151.4, 154.0, 166.1, 202.4.

MS (ESI): *m*/*z* = 406 $[M + Na]^+$.

9,10-Dimethoxy-5*H*-[1,3]dioxolo[4′′,5′′:4′,5′]benzo[1′,2′:4,5]azepino[2,1-*a*]isoindole-8,13(6*H*,12b*H*)-dione (Deoxychilenine, 2)

To a stirred soln of **10** (100 mg, 0.25 mmol) and Et_3SiH (0.12 mL, 0.75 mmol) in CH_2Cl_2 (5 mL) was added $BF_3{\cdot}OEt_2$ (0.10 mL) at –10 °C in a dropwise fashion. The mixture was further stirred for 20 min at the same temperature and then quenched by addition of a few drops of sat. aq $NaHCO_3$. EtOAc (20 mL) was added to the mixture and the organic layer was washed with H_2O (10 mL) and brine (10 mL), and dried (Na_2SO_4). Concentration of organic layer in vacuo followed by column chromatography (silica gel, PE–EtOAc, 4:6) furnished **2** (89 mg, 96%) as a white solid; mp 155 °C (Lit.[4c] 156–157 °C).

IR ($CHCl_3$): 1694, 1613 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.01 (ddd, *J* = 15, 4, 2 Hz, 1 H), 3.25 (dt, *J* = 14, 4 Hz, 1 H), 3.59 (ddd, *J* = 14, 6, 2 Hz, 1 H), 3.90 (s, 3 H), 4.02 (s, 3 H), 4.27 (dt, *J* = 14, 4 Hz, 1 H), 5.15 (s, 1 H, not exchangeable with D_2O), 6.00 (d, *J* = 2 Hz, 2 H), 6.71 (s, 1 H), 6.90 (s, 1 H), 7.18 (d, *J* = 8 Hz, 1 H), 7.58 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.5, 41.3, 56.6, 62.5, 65.9, 101.9, 108.6, 109.3, 116.5, 120.1, 124.1, 131.2, 132.3, 133.8, 146.5, 147.2, 151.6, 153.1, 167.4, 201.0.

MS (ESI): *m*/*z* = 390 $[M + Na]^+$.

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