Synthesis of the Reported Protoberberine Gusanlung D

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Abstract: Starting from homopiperonylamine or phenethylamine with homophthalic anhydride or 3,4-methylenedioxyhomophthalic acid, respectively, facile syntheses of the reported structures of (±)-gusanlung D and (±)-isogusanlung D were accomplished via regioselective reductive dehydration of the corresponding homophthalimides followed by an intramolecular acid-catalyzed or radical cyclization pathway. Starting from the corresponding suitably *ortho*-halogenated homophthalimides, the syntheses of dehydrogusanlung and dehydroisogusanlung D were completed via regioselective reductive dehydration followed by an intramolecular Heck coupling reaction as the key steps. The analytical and spectral data obtained for all four synthetic compounds differed from the reported data for natural gusanlung D, and therefore the structural assignment of the natural product needs to be revised.

Key words: homophthalic anhydride, homopiperonyl amine, reductive dehydration, Heck reaction, gusanlung D

Protoberberine alkaloids make up an important class of natural products that contain a tetracyclic ring skeleton with an isoquinoline core[1] possessing anti-inflammatory, antimicrobial, antileukemic, and antitumor activities.[2] Many elegant achiral and chiral synthetic routes to protoberberines have been reported in the literature.[2,3] The isolation of (–)-gusanlung D (2,3-methylenedioxy-8-oxoberberine, **1**; Scheme 1) from the stem of *Acangelisia gusanlung* was reported in 1995 by Zhong et al.; this is the first optically active protoberberine unoxygenated at ring D.[4] Well before the isolation of gusanlung D, Kesser et al. from India reported its racemic synthesis via the generation and trapping of α-oxo-*o*-quinodimethanes.[5] Unfortunately, the analytical and spectral data reported for the natural and synthetic gusanlung D were not in agreement with one other.[4,5] Padwa and Waterson reported a neat approach to berberine derivative (±)-**1** by taking advantage of a Pummerer/Mannich-induced cyclization cascade.[6] Recently, Reimann et al. reported the synthesis of (±)-gusanlung D from the Reissert compounds.[7] Very recently, Chang and Chang reported the synthesis of (±)-gusanlung D via dehydrogusanlung D (**2**; Scheme 1), by taking advantage of ring-closing metathesis.[8] Chrzanowska et al. reported the first asymmetric synthesis of both (+)- and (–)-gusanlung D, indicating the possibility of considerable contamination of the natural product with dehydrogusanlung D (**2**).[9]

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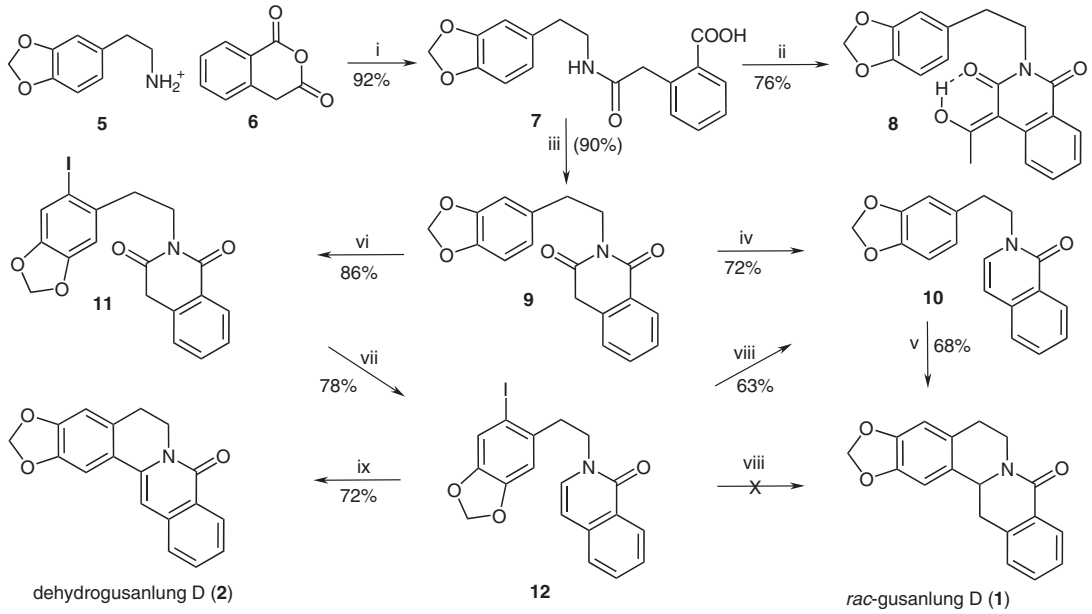
During the past several years, we have been using cyclic anhydrides as potential precursors for the synthesis of structurally interesting and biologically important natural and unnatural products.[10] As the unconjugated carbonyl group in the homophthalic anhydride/imide can be regioselectively explored, we reasoned that homophthalic anhydride or imide would be the most appropriate building block for the synthesis of protoberberine alkaloids. Herein we report a general strategy for the synthesis of protoberberine alkaloids starting from homophthalic anhydride or imide, to synthesize the reported (±)-gusanlung D (**1**), (±)-isogusanlung D (**3**), dehydrogusanlung D (**2**), and dehydroisogusanlung D (**4**) by three different modes of intramolecular cyclization (Schemes 1 and 2).

The regioselective ring opening of homophthalic anhydride (**6**) at the more reactive unconjugated carbonyl with homopiperonylamine (**5**) in a diethyl ether–tetrahydrofuran mixture at room temperature exclusively furnished benzoic acid **7** in 92% yield (Scheme 1). An attempted preparation of the corresponding isoquinoline-1,3(2*H*,4*H*)-dione **9** by dehydration of **7** induced by acetic anhydride–sodium acetate resulted instead in the formation of 3-hydroxyisoquinolin-1(2*H*)-one **8** bearing an α-acyl substituent in 76% yield (Scheme 1), formed due to the highly acidic nature of the α-methylene protons of such systems. A singlet signal at δ = 11.05 and the corresponding absence of a methylene proton signal in the ^{1}H NMR spectrum of the above product clearly revealed that the product existed exclusively as the enol **8**, which is stabilized by conjugation of the double bond with the carbonyl group and the phenyl ring as well as by intramolecular hydrogen bonding. Ultimately, acid **7** on treatment with hexamethyldisilazane–zinc(II) chloride[11] gave the desired isoquinoline-1,3(2*H*,4*H*)-dione **9** in 90% yield (Scheme 1).

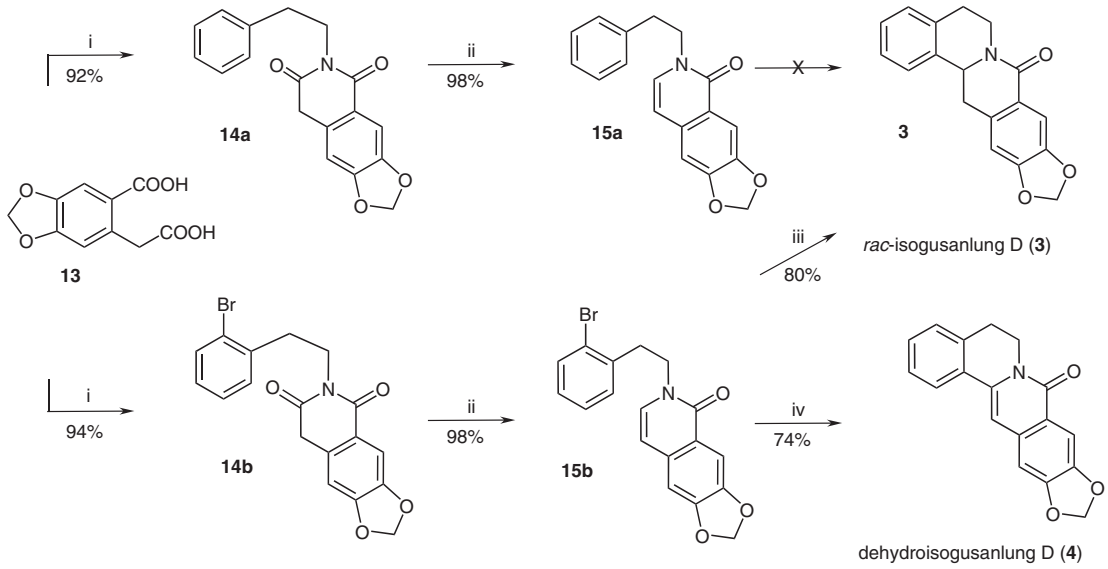
We envisaged a regioselective reduction of the unconjugated carbonyl in imide **9** to provide the corresponding hydroxylactam, which upon intramolecular cyclization would provide us with the desired racemic protoberberine (±)-**1** (Scheme 1). Interestingly, when we carried out the sodium borohydride reduction of **9** under the conditions reported by Speckamp et al.,[12] the expected hydroxylactam formed as an intermediate, directly furnishing the isoquinolin-1(2*H*)-one **10** in 72% yield by an in situ dehydration. The formation of **10** constitutes a formal synthesis of (±)-gusanlung D (**1**), since **10** is a known precursor that can be easily transformed into the protoberberine, as demonstrated by Padwa and Waterson.[6] We employed their acid-catalyzed cyclization conditions to



Scheme 1 *Reagents and conditions*: (i) Et_2O–THF (4:1), r.t., 2 h (92%); (ii) Ac_2O, NaOAc, 60 °C, 3 h (76%); (iii) HMDS, $ZnCl_2$, benzene, 2.5 h (90%); (iv) (a) $NaBH_4$, EtOH, 0 °C, 6 h; (b) H^+/HCl, r.t., 12 h (72%); (v) concd HCl, r.t., 48 h (68%); (vi) I_2, AgO_2CCF_3, $CHCl_3$, r.t., 8 h (86%); (vii) (a) $NaBH_4$, EtOH, 0 °C, 6 h; (b) H^+/HCl, r.t., 12 h (78%); (viii) AIBN, Bu_3SnH, benzene, reflux, 6 h (63%); (ix) $Pd(OAc)_2$, tetramethylguanidine, NaOAc, DMF, 110 °C, 20 h (72%).

convert enamide **10** into (±)-gusanlung D (**1**) in 68% yield (Scheme 1). However, the analytical and spectral data for compound **1** synthesized by us did not match those reported for the isolated natural product, but were in full agreement with those reported in the earlier syntheses.[5–9] Chrzanowska et al. had opined that the discrepancy could have arisen due to a possible contamination of the isolated natural product with a considerable amount of the corresponding oxidized product dehydrogusanlung D (**2**),[8] formed during the isolation process. Therefore, we planned to synthesize dehydrolactam **12** by a route that had the potential to deliver (±)-gusanlung D (**1**) as well.

Towards this end, a very selective iodination of imide **9** by iodine–silver trifluoroacetate was used, affording isoquinoline-1,3(2*H*,4*H*)-dione **11** in 86% yield (Scheme 1). As expected, the sodium borohydride reduction of **11**, under the Speckamp et al. conditions as before, furnished isoquinolin-1(2*H*)-one **12** in 78% yield. Compound **12** could potentially serve as a precursor to both (±)-gusanlung D (**1**), through an intramolecular radical cyclization, as well as dehydrogusanlung D (**2**), via an intramolecular Heck coupling reaction (Scheme 1).[13] Unfortunately, our attempts at intramolecular radical cyclization of **12** using the standard conditions consisting of azoisobutyronitrile



Scheme 2 *Reagents and conditions*: (i) $Ph(CH_2)_2NH_2$ (for **14a**) or 2-$BrC_6H_4(CH_2)_2NH_2$ (for **14b**), 1,2-dichlorobenzene, 180 °C, 3 h (92/94%); (ii) (a) $NaBH_4$, EtOH, 0 °C, 6 h; (b) H^+/HCl, r.t., 12 h (98%); (iii) AIBN, Bu_3SnH, benzene, reflux, 2 h (80%); (iv) $Pd(OAc)_2$, TBAB, K_2CO_3, DMF, 120 °C, 24 h (74%).

and tributyltin hydride failed to deliver the protoberberine (±)-**1**; we ended up instead with the dehalogenated product **10** in 63% yield (Scheme 1). We were, nevertheless, successful in carrying out a palladium(II) acetate–tetramethylguanidine induced[14] intramolecular Heck coupling of isoquinolin-1(2*H*)-one **12**, and obtained the desired dehydrogusanlung D (**2**) in 72% yield (Scheme 1). The analytical and spectral data obtained for **2** were in complete agreement with the reported data.[8] However, a comparison of the analytical and spectral data of compound **2** with those of gusanlung D (**1**) and those reported for the isolated natural product ruled out the possibility that the isolated product could have been contaminated with a considerable amount of **2**.

At this stage, on the basis of the ^{1}H NMR data for reported natural **1** (a singlet at δ = 7.35 for one of the aromatic protons), we felt that there is a possibility that the isolated natural product could be the isomeric compound **3** (*peri* interaction with the carbonyl group), and we planned to synthesize both (±)-isogusanlung D (**3**) and dehydroisogusanlung D (**4**) (Scheme 2). The thermal double dehydrative condensation of phenethylamine or 2-bromophenethylamine with 3,4-methylenedioxyhomophthalic acid **13**[15] gave the corresponding imides **14a** and **14b**, respectively, in high yields (Scheme 2). The regioselective reductive dehydration of both the imides **14a** and **14b** provided the required isoquinolinone derivatives **15a** and **15b**, respectively, in 98% yield. All our attempts to induce acid-catalyzed intramolecular cyclization of **15a** to form (±)-isogusanlung D (**3**) met with failure, because of the absence of any activating group on phenyl ring, required to force such type of cyclizations. However, treatment of aryl bromide **15b** with azoisobutyronitrile–tributyltin hydride resulted in intramolecular radical cyclization,[16] to furnish the desired (±)-isogusanlung D (**3**) in 74% yield, while Heck coupling of **15b** gave the corresponding dehydroisogusanlung D (**4**) in 80% yield (Scheme 2). Unfortunately, in this case too, the obtained analytical and spectral data for **3** and **4** did not match the data reported for the natural product **1**.

In summary, we have developed a general approach to protoberberine alkaloids starting from homophthalic anhydride, and accomplished a facile synthesis of the claimed gusanlung D and isogusanlung D via an efficient regioselective reductive dehydration followed by acid-catalyzed or radical-induced intramolecular cyclizations, respectively. Similarly, the synthesis of the corresponding dehydrogusanlung D and dehydroisogusanlung D were completed by taking advantage of an elegant intramolecular Heck coupling reaction. Unfortunately, the analytical and spectral data obtained for all four berberine analogues did not concur with the reported data of the natural product. At this point, we feel that revision of the reported structural assignment of gusanlung D needs to be undertaken, and that it would be more appropriate to re-establish the actual structure of the natural product gusanlung D on the basis of X-ray crystallographic analysis.

Melting points are uncorrected. ^{1}H NMR spectra of samples in $CDCl_3$ and DMSO-d_6 with TMS as an internal standard were recorded on 200- and 400-MHz spectrometers. ^{13}C NMR spectra were recorded on 200-, 400- and 500-MHz NMR spectrometers (at 50, 100, and 125 MHz, respectively, for ^{13}C). IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were done on silica gel (60–120, 230–300 mesh). Commercially available homophthalic anhydride (**6**), 2-bromophenethylamine, HMDS, $ZnCl_2$, silver trifluoroacetate, Bu_3SnH, and $Pd(OAc)_2$ were used.

2-(2-{[2-(1,3-Benzodioxol-5-yl)ethyl]amino}-2-oxoethyl)benzoic Acid (7)

A soln of homopiperonylamine (**5**; 2.48 g, 15.00 mmol) in Et_2O (15 mL) was added dropwise over 15 min to a constantly stirring soln of homophthalic anhydride (**6**; 2.43 g, 15.00 mmol) in a mixture of Et_2O–THF (4:1, 15 mL). The reaction mixture was stirred for 2 h at r.t. and the precipitated crystalline product was filtered, washed with Et_2O (30 mL), and dried in vacuo; this gave **7**.

Yield: 4.52 g (92%); mp 155–157 °C (Lit.[17] 158–159 °C).

IR ($CHCl_3$): 3346, 1700, 1694 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.64 (t, *J* = 7 Hz, 2 H), 3.26 (q, *J* = 7 Hz, 2 H), 3.86 (s, 2 H), 5.97 (s, 2 H), 6.65 (dd, *J* = 8, 2 Hz, 1 H), 6.80 (s, 1 H), 6.82 (d, *J* = 10 Hz, 1 H), 7.26 (dd, *J* = 10, 2 Hz, 1 H), 7.36 (dt, *J* = 8, 2 Hz, 1 H), 7.49 (dt, *J* = 8, 2 Hz, 1 H), 7.86 (dd, *J* = 8, 2 Hz, 1 H), 7.98 (t, *J* = 6 Hz, 1 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 35.2, 40.8, 40.9, 100.9, 108.4, 109.4, 121.9, 127.0, 130.5, 131.6, 131.9 (2 C), 133.6, 137.2, 145.8, 147.5, 169.0, 170.5.

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.96; H, 5.11; N, 4.35.

4-Acetyl-2-[2-(1,3-benzodioxol-5-yl)ethyl]-3-hydroxyisoquinolin-1(2*H*)-one (8)

A stirred mixture of **7** (490 mg, 1.50 mmol) in Ac_2O (10 mL) and fused NaOAc (20 mg, 0.24 mmol) was heated at 60 °C for 3 h. The mixture was allowed to reach r.t. and was then poured into ice-cold H_2O. The precipitate that formed was filtered, washed with an excess of H_2O, and vacuum-dried; this gave **8**.

Yield: 400 mg (76%); mp 112–114 °C.

IR ($CHCl_3$): 3311, 1739, 1648 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.57 (s, 3 H), 2.88 (t, *J* = 7 Hz, 2 H), 3.73 (app q, *J* = 7 Hz, 2 H), 5.92 (s, 2 H), 6.60–6.80 (m, 3 H), 7.10–7.25 (m, 1 H), 7.50–7.70 (m, 2 H), 8.16 (d, *J* = 8 Hz, 1 H), 11.05 (bs, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.0, 35.5, 42.7, 92.4, 100.8, 108.2, 108.9, 114.8, 121.6, 123.3, 123.4, 130.2, 131.5, 134.8, 138.7, 146.2, 147.7, 158.6, 160.9, 194.2.

Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.57; H, 4.93; N, 4.05.

2-[2-(1,3-Benzodioxol-5-yl)ethyl]isoquinoline-1,3(2*H*,4*H*)-dione (9)

To a stirred suspension of **7** (3.92 g, 12.00 mmol) in anhyd benzene (30 mL) was added $ZnCl_2$ (1.64 g, 12.00 mmol) and the mixture was heated at 80 °C. To this mixture was slowly added a soln of HMDS (3.75 mL, 18.00 mmol) in anhyd benzene (15 mL) over 20 min. The mixture was refluxed for an additional 2 h, then cooled to r.t. and poured into 1 N HCl (30 mL). The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic layer was washed with 5% aq $NaHCO_3$ (3 × 20 mL) and brine (25 mL), and dried (Na_2SO_4). Concentration of the organic layer in vacuo fol-

lowed by purification of the residue by column chromatography (silica gel, PE–EtOAc, 4:1) gave pure **9**.

Yield: 3.34 g (90%); mp 158–159 °C (Lit.[17] 156–157 °C).

IR ($CHCl_3$): 1709, 1662, 1607 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.75–2.90 (m, 2 H), 4.03 (s, 2 H), 4.05–4.25 (m, 2 H), 5.92 (s, 2 H), 6.65–6.85 (m, 3 H), 7.28 (d, *J* = 8 Hz, 1 H), 7.45 (t, *J* = 8 Hz, 1 H), 7.60 (dt, *J* = 8, 2 Hz, 1 H), 8.22 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.7, 36.3, 41.6, 100.7, 108.1, 109.3, 121.7, 125.2, 127.0, 127.6, 129.0, 132.2, 133.5, 134.0, 146.0, 147.5, 164.6, 169.7.

Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 70.02; H, 4.81; N, 4.59.

2-[2-(1,3-Benzodioxol-5-yl)ethyl]isoquinolin-1(2*H*)-one (10)

Excess $NaBH_4$ (304 mg, 8.00 mmol) was added to a stirred soln of **9** (309 mg, 1.00 mmol) in EtOH (10 mL) at 0 °C. The mixture was stirred under inert atmosphere for 6 h at 0 °C while 2–3 drops of 2 N HCl in EtOH were added at intervals of 20 min. The excess of $NaBH_4$ was then quenched at 0 °C by the addition of 2 N HCl in EtOH until the mixture was acidic (pH 3). The mixture was then allowed to warm to r.t. and stirred for a further 12 h. The EtOH was removed by distillation under reduced pressure, the residue was diluted with H_2O (20 mL), and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with H_2O (20 mL), 5% aq $NaHCO_3$ (20 mL), and brine (20 mL) and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by purification of the residue by column chromatography (silica gel, PE–EtOAc, 4:1) gave **10**.

Yield: 211 mg (72%); mp 87–88 °C (Lit.[6] 90–91 °C).

IR ($CHCl_3$): 1649, 1626 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.00 (t, *J* = 8 Hz, 2 H), 4.16 (t, *J* = 8 Hz, 2 H), 5.93 (s, 2 H), 6.39 (d, *J* = 8 Hz, 1 H), 6.60–6.75 (m, 3 H), 6.81 (d, *J* = 8 Hz, 1 H), 7.40–7.55 (m, 2 H), 7.55–7.70 (m, 1 H), 8.45 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.9, 51.6, 100.8, 105.6, 108.3, 109.2, 121.8, 125.8, 126.1, 126.6, 127.6, 131.9 (2 C), 132.0, 137.0, 146.2, 147.7, 161.9.

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.59; H, 5.22; N, 4.59.

2-[2-(6-Iodo-1,3-benzodioxol-5-yl)ethyl]isoquinoline-1,3(2*H*,4*H*)-dione (11)

I_2 (775 mg, 3.05 mmol) was added in small portions over 15 min to a stirring soln of **9** (943 mg, 3.05 mmol) and AgO_2CCF_3 (674 mg, 3.05 mmol) in anhyd $CHCl_3$ (15 mL). The mixture was stirred for a further 8 h at r.t. The mixture was filtered, washed with CH_2Cl_2 (25 mL) and the filtrate was washed with 5% aq $Na_2S_2O_3$ (10 mL), H_2O (20 mL), and brine (25 mL) and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by purification of the residue by column chromatography (silica gel, PE–EtOAc, 4:1) gave **11**.

Yield: 1.14 g (86%); mp 217–219 °C.

IR ($CHCl_3$): 1701, 1668, 1609 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.90–3.10 (m, 2 H), 4.04 (s, 2 H), 4.10–4.25 (m, 2 H), 5.95 (s, 2 H), 6.85 (s, 1 H), 7.22 (s, 1 H), 7.25–7.35 (m, 1 H), 7.45 (t, *J* = 8 Hz, 1 H), 7.60 (dt, *J* = 8, 2 Hz, 1 H), 8.22 (dd, *J* = 8, 2 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 36.4, 38.6, 40.2, 87.7, 101.5, 109.7, 118.6, 125.3, 127.1, 127.7, 129.1, 133.6, 134.1, 135.0, 147.2, 148.5, 164.7, 169.8.

Anal. Calcd for $C_{18}H_{14}INO_4$: C, 49.68; H, 3.24; N, 3.22. Found: C, 49.53; H, 3.15; N, 3.10.

2-[2-(6-Iodo-1,3-benzodioxol-5-yl)ethyl]isoquinolin-1(2*H*)-one (12)

Compound **12** was prepared from **11** (1.09 g, 2.51 mmol) by the same procedure as described above for the preparation of **10** from **9**.

Yield: 819 mg (78%); mp 165–167 °C.

IR ($CHCl_3$): 1651, 1626, 1599 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.14 (t, *J* = 8 Hz, 2 H), 4.15 (t, *J* = 8 Hz, 2 H), 5.94 (s, 2 H), 6.43 (d, *J* = 8 Hz, 1 H), 6.75 (s, 1 H), 6.94 (d, *J* = 6 Hz, 1 H), 7.24 (s, 1 H), 7.40–7.70 (m, 3 H), 8.46 (dd, *J* = 8, 2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 39.6, 49.6, 87.8, 101.6, 105.9, 110.2, 118.6, 125.9, 126.1, 126.8, 127.7, 131.7, 132.1, 134.0, 137.0, 147.4, 148.7, 162.1.

Anal. Calcd for $C_{18}H_{14}INO_3$: C, 51.57; H, 3.37; N, 3.34. Found: C, 51.42; H, 3.48; N, 3.29.

6-Phenethyl[1,3]dioxolo[4,5-*g*]isoquinoline-5,7(6*H*,8*H*)-dione (14a)

A stirring soln of $Ph(CH_2)_2NH_2$ (108 mg, 0.89 mmol) and **13** (200 mg, 0.89 mmol) in 1,2-dichlorobenzene (10 mL) was refluxed at 180 °C for 3 h. After the mixture had cooled to r.t., it was loaded on a silica gel column [PE (removal of 1,2-dichlorobenzene), then PE–EtOAc, 4:1]; this furnished **14a** as a yellow crystalline solid.

Yield: 253 mg (92%); mp 110–112 °C.

IR ($CHCl_3$): 1711, 1665, 1622 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.84–2.96 (m, 2 H), 3.91 (s, 2 H), 4.12–4.23 (m, 2 H), 6.07 (s, 2 H), 6.65 (s, 1 H), 7.16–7.34 (m, 5 H), 7.59 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.0, 36.4, 41.4, 102.0, 106.3, 107.8, 119.4, 126.4, 128.4, 128.9, 130.3, 138.6, 147.7, 152.5, 164.0, 169.7.

Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 70.02; H, 4.63; N, 4.40.

6-Phenethyl[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (15a)

Compound **15a** was prepared from **14a** (150 mg, 0.49 mmol) by the same procedure as described above for the preparation of **10** from **9**.

Yield: 139 mg (98%); mp 107–109 °C.

IR ($CHCl_3$): 1657, 1620, 1606 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.07 (t, *J* = 8 Hz, 2 H), 4.18 (t, *J* = 8 Hz, 2 H), 6.07 (s, 2 H), 6.25 (d, *J* = 8 Hz, 1 H), 6.70 (d, *J* = 8 Hz, 1 H), 6.82 (s, 1 H), 7.14–7.34 (m, 5 H), 7.80 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 35.3, 51.5, 101.6, 103.6, 105.5, 105.6, 121.7, 126.5, 128.6, 128.9, 130.7, 134.3, 138.3, 147.8, 151.7, 161.2.

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.68; H, 5.11; N, 4.97.

6-(2-Bromophenethyl)[1,3]dioxolo[4,5-*g*]isoquinoline-5,7(6*H*,8*H*)-dione (14b)

Compound **14b** was prepared from 2-$BrC_6H_4(CH_2)_2NH_2$ (446 mg, 2.23 mmol) and **13** (500 mg, 2.23 mmol) by the same procedure as described above for the preparation of **14a** from **13** and $Ph(CH_2)_2NH_2$.

Yield: 814 mg (94%); mp 134–136 °C.

IR ($CHCl_3$): 1709, 1665, 1657, 1649, 1618 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.00–3.15 (m, 2 H), 3.90 (s, 2 H), 4.15–4.30 (m, 2 H), 6.06 (s, 2 H), 6.65 (s, 1 H), 7.00–7.32 (m, 3 H), 7.53 (dd, *J* = 8, 2 Hz, 1 H), 7.58 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.1, 36.4, 39.6, 102.0, 106.3, 107.7, 119.3, 124.6, 127.4, 128.1, 130.2, 130.9, 132.7, 138.2, 147.6, 152.4, 163.9, 169.7.

Anal. Calcd for $C_{18}H_{14}BrNO_4$: C, 55.69; H, 3.63; N, 3.61. Found: C, 55.55; H, 3.47; N, 3.80.

6-(2-Bromophenethyl)[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (15b)

Compound **15b** was prepared from **14b** (600 mg, 1.54 mmol) by the same procedure as described above for the preparation of **10** from **9**.

Yield: 563 mg (98%); mp 153–155 °C.

IR ($CHCl_3$): 1655, 1618, 1605 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.23 (t, *J* = 8 Hz, 2 H), 4.22 (t, *J* = 8 Hz, 2 H), 6.08 (s, 2 H), 6.27 (d, *J* = 6 Hz, 1 H), 6.76 (d, *J* = 6 Hz, 1 H), 6.83 (s, 1 H), 7.04–7.21 (m, 3 H), 7.56 (d, *J* = 8 Hz, 1 H), 7.81 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 35.3, 49.2, 101.5, 103.5, 105.3, 105.5, 121.5, 124.3, 127.6, 128.3, 130.5, 131.3, 132.7, 134.2, 137.4, 147.6, 151.5, 161.1.

Anal. Calcd for $C_{18}H_{14}BrNO_3$: C, 58.08; H, 3.79; N, 3.76. Found: C, 57.94; H, 3.65; N, 3.69.

5,6,13,13a-Tetrahydro-8*H*-[1,3]dioxolo[4,5-*g*]isoquino[3,2-*a*]isoquinolin-8-one [(±)-Gusanlung D, 1]

A soln of **10** (147 mg, 0.50 mmol) in concd HCl (5 mL) was stirred at r.t. for 48 h. The mixture was then diluted with ice water (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed successively with 5% aq $NaHCO_3$ (20 mL) and brine (20 mL) and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by purification of the residue by column chromatography (silica gel, PE–EtOAc, 4:1) gave (±)-gusanlung D (**1**).

Yield: 100 mg (68%); mp 194–196 °C [Lit.[4] 250–251 °C (natural), Lit.[9] 195–197 °C (synthetic)].

IR ($CHCl_3$): 1647 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.70–2.80 (m, 1 H), 2.85–3.05 (m, 3 H), 3.18 (dd, *J* = 16, 4 Hz, 1 H), 4.83 (dd, *J* = 13, 4 Hz, 1 H), 4.90–5.00 (m, 1 H), 5.96 (s, 2 H), 6.67 (s, 1 H), 6.72 (s, 1 H), 7.24 (d, *J* = 8 Hz, 1 H), 7.39 (t, *J* = 8 Hz, 1 H), 7.46 (t, *J* = 8 Hz, 1 H), 8.13 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.7, 38.1, 38.8, 55.3, 101.1, 105.9, 108.7, 126.9, 127.3, 128.5, 128.6, 128.9, 129.1, 131.8, 137.2, 146.6, 146.8, 164.6.

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.56; H, 5.28; N, 4.81.

5,6-Dihydro-8*H*-[1,3]dioxolo[4,5-*g*]isoquino[3,2-*a*]isoquinolin-8-one (Dehydrogusanlung D, 2)

A soln of $Pd(OAc)_2$ (0.5 mg, 0.25 mol%) and tetramethylguanidine (1 mg, 1 mol%) in DMF (10 mL) was added to an argon-flushed flask containing **12** (335 mg, 0.80 mmol) and NaOAc (98.5 mg, 1.20 mmol), and the mixture was stirred at 120 °C for 20 h. After cooling to r.t., the mixture was poured into H_2O (20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with brine (20 mL) and dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by purification of the residue by column chromatography (silica gel, PE–EtOAc, 4:1) furnished **2**.

Yield: 168 mg (72%); mp 181–182 °C (Lit.[8] 183–184 °C).

IR ($CHCl_3$): 1715, 1645, 1616 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.91 (t, *J* = 6 Hz, 2 H), 4.33 (t, *J* = 6 Hz, 2 H), 6.01 (s, 2 H), 6.71 (s, 1 H), 6.83 (s, 1 H), 7.25 (s, 1 H), 7.43 (t, *J* = 8 Hz, 1 H), 7.53 (d, *J* = 8 Hz, 1 H), 7.62 (t, *J* = 8 Hz, 1 H), 8.41 (d, *J* = 8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5, 39.7, 101.5, 101.9, 105.0, 107.9, 123.7, 124.6, 126.0, 126.3, 127.9, 130.3, 132.3, 136.6, 137.4, 147.4, 148.7, 162.1.

Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.31; H, 4.47; N, 4.96.

5,6,14,14a-Tetrahydro-8*H*-[1,3]dioxolo[4,5-*g*]isoquino[2,1-*b*]isoquinolin-8-one [(±)-Isogusanlung D, 3]

A soln of Bu_3SnH (0.3 mL, 1.07 mmol) and AIBN (9 mg, 0.05 mmol) in benzene (5 mL) was added dropwise over 5 min to a constantly stirring, refluxing soln of **15b** (200 mg, 0.53 mmol) in benzene (10 mL) under a N_2 atmosphere. The mixture was refluxed for an additional 2 h. Then the mixture was cooled to r.t. and the benzene solvent was removed in vacuo. The residue thus obtained was then dissolved in MeCN (20 mL) and washed with *n*-hexane (3 × 25 mL). Concentration of the MeCN layer in vacuo followed by purification of the residue by column chromatography (silica gel, PE–EtOAc, 7:3) furnished pure **3** as a white crystalline solid.

Yield: 116 mg (74%); mp 157–159 °C.

IR ($CHCl_3$): 1639, 1611 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.80–3.07 (m, 4 H), 3.14 (dd, *J* = 12, 4 Hz, 1 H), 4.84–5.00 (m, 2 H), 6.02 (d, *J* = 4 Hz, 2 H), 6.69 (s, 1 H), 7.15–7.35 (m, 4 H), 7.59 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.6, 37.7, 38.5, 55.1, 101.4, 106.7, 108.3, 123.1, 125.8, 126.6, 126.7, 128.9, 132.8, 134.9, 135.7, 146.9, 150.4, 164.1.

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.57; H, 5.05; N, 4.66.

5,6-Dihydro-8*H*-[1,3]dioxolo[4,5-*g*]isoquino[2,1-*b*]isoquinolin-8-one (Dehydroisogusanlung D, 4)

K_2CO_3 (438 mg, 3.18 mmol), TBAB (346 mg, 1.07 mmol), and $Pd(OAc)_2$ (11 mg, 10 mol%) were added to a stirred soln of **15b** (200 mg, 0.53 mmol) in DMF (10 mL) at r.t. under a N_2 atmosphere. Then the mixture was heated at 120 °C for 24 h, before it was cooled to r.t. and diluted with EtOAc (20 mL), washed with brine, and finally dried (Na_2SO_4). Concentration of the organic layer in vacuo followed by purification of the residue by column chromatography (silica gel, PE–EtOAc, 7:3) furnished compound **4** as a yellow crystalline solid.

Yield: 125 mg (80%); mp 174–175 °C.

IR ($CHCl_3$): 1649, 1605 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.95–3.05 (m, 2 H), 4.30–4.40 (m, 2 H), 6.07 (s, 2 H), 6.91 (s, 2 H), 7.20–7.40 (m, 3 H), 7.70–7.80 (m, 1 H), 7.79 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.2, 39.3, 101.4, 102.5, 103.5, 105.3, 120.2, 124.4, 127.1, 127.7, 128.8, 129.8, 133.5, 134.8, 135.8, 147.4, 151.5, 160.9.

Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.37; H, 4.42; N, 4.89.

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