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Synthesis of Homoprotoberberines and 8-Oxoprotoberberines by Sequential Bicyclization of Phenylacetamides

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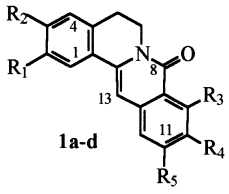
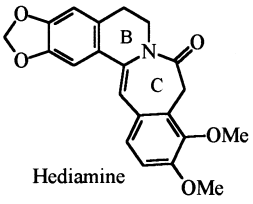
Abstract—The reaction of phenylacetamides with oxalyl chloride/Lewis acid provides a convergent, high-yield entry to C-homoprotoberberine and 8-oxoprotoberberine alkaloids from available starting materials. This approach was used to synthesize 8-oxopseudopalmatine starting from *N*-[β-(3′,4′-dimethoxyphenyl)ethyl]-3,4-dimethoxyphenylacetamide. Some C-homoprotoberberines exhibit significant cytotoxicity against human breast carcinoma cells.

Protoberberines constitute an important group of isoquinoline alkaloids on account of their physiological activity.[1] A wide array of substituents in the tetracyclic system are known that include 8-oxoprotoberberines (**1a**,**c**,**d**). Some of them were recently isolated from natural sources,[2] some exhibit antiulcerative properties (8-oxocoptisine, **1d**)[3] and others inhibit the sodium current in human atrial myocytes (8-oxoberberine, **1c**).[4]



1a-d

	R_1	R_2	R_3	R_4	R_5
(1a)	OMe	OMe	H	OMe	OMe
(1b)	OMe	OMe	H	OMe	H
(1c)	OCH_2O		OMe	OMe	H
(1d)	OCH_2O		OCH_2O		H



Hediamine

C-Homoprotoberberines such as hediamine have been isolated from natural sources;[5] however, these alkaloids can be regarded as artefacts produced during the isolation process rather than as naturally occurring compounds.[5a]

From a synthetic point of view, 8-oxoprotoberberines are major intermediates in the synthesis of other protoberberine alkaloids;[1a,6] various approaches to their total synthesis have been developed. Formation of rings B and C in the final steps is the approach of choice. Ring B has generally been constructed by variants of the Bischler–Napieralski cyclization[1a,7] and ring C in many different ways including: (i) photochemical cyclization of 1-methyleneisoquinolines[8] (or by Heck reaction)[9] or stilbene derivatives;[10] (ii) reaction of isoquinoline derivatives with arynes,[11] phthalides,[12] homophthalic anhydrides[13] or silyl derivatives;[14] and (iii) from Reissert compounds.[15]

Recently, the synthesis of 8-oxopseudopalmatine (**1a**) was accomplished with a 50% yield by one-pot reaction of the corresponding *N*-ethoxycarbonyl-phenylethylamine with homoveratric acid in polyphosphoric acid.[16] The simultaneous formation of rings B and C has also been accomplished by oxidation of an appropriate 10-membered ring macrolactam with *m*-chloroperbenzoic acid to give the unsubstituted skeleton.[17]

We have developed a new, short synthesis for the cytotoxic isoquinoline alkaloids, 4,5-dioxoaporphines, 3,4-dioxocularines (**2**) and aristocularines (**3**) by sequential bicyclization of suitably substituted arylacetamides promoted by oxalyl chloride and tin(IV) chloride.[18] In this cyclization, oxalyl chloride generates the 2-chloro-oxazolidine-4,5-dione (**I**) precursor of the electrophilic *N*-acyliminium ion and acts as an α-dicarbonyl or monocarbonyl transfer agent (Scheme 1).

We envisaged that this approach could be applied to the cyclization of phenylethyl phenylacetamides (Scheme 2) to provide a direct access to ring C-homoprotoberberines and 8-oxoprotoberberines provided decarbonylation occurred under the prevailing reaction conditions.

Keywords: homoprotoberberines; phenylacetamides; alkaloids; isoquinolines; cytotoxicity; oxalyl chloride.

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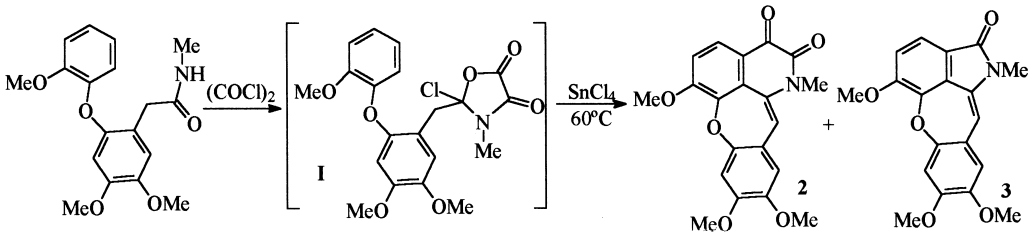
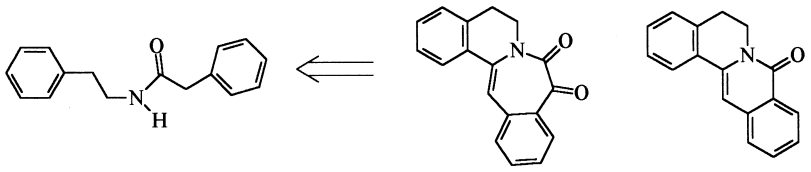


Scheme 1.



Scheme 2.

This paper describes in detail the reaction of various *N*-[β-(phenyl)ethyl]-phenylacetamides with oxalyl chloride/Lewis acid to afford ring C-homoprotoberberines in a single step by sequential formation of rings B and C. We also report a straightforward synthesis for 8-oxoprotoberberines from ring C-homoprotoberberines by either thermal decarbonylation or decarboxylation after benzylic acid type of rearrangement.

Results and Discussion

According to Larsen,[19] the reaction of (1,2-diphenylethyl)-phenylacetamide (**4**) with oxalyl chloride and $FeCl_3$, in a modified Bischler–Napieralski process, gives the oxalyl adduct **5** in 55% yield. Acid hydrolysis of this oxazolidindione affords the corresponding 3,4-dihydroisoquinoline (**6**) (Scheme 3).

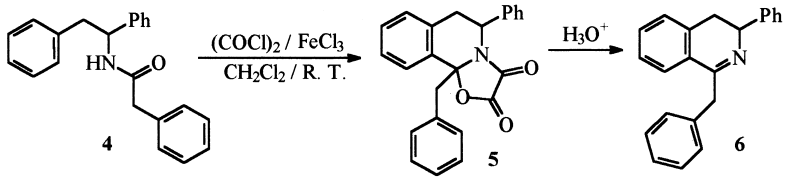
In our study, and under similar conditions [$(COCl)_2/SnCl_4$ at room temperature], the amide **7a** gave the related oxazolidindione **8a** in a 63% yield. However, we knew from previous work that this type of oxalyl adducts is readily opened if a proton can be eliminated from a benzylic position by increasing the reaction temperature. Thus, when the reaction of **7a** was carried out at 60°C (2 equiv. of $SnCl_4$), the yield of **8a** decreased to 8%. At this temperature, and in the presence of $BF_3{\cdot}OEt_2$ as Lewis acid, opening of the oxazolidinedione and a second cyclization easily occur and provide an almost quantitative yield of the expected C-homoprotoberberine (**9a**). FAB-MS was consistent with the proposed homoprotoberberine structure, **9a**, and exhibited two carbonyl signals and four uncoupled aromatic protons in the CMR and the PMR spectrum, respectively (Scheme 4).

With a less active aromatic ring D (**7b**), the yield of homoprotoberberine (**9b**) was lower (65%). When the aromatic portion of the phenylacetic acid moiety is unsubstituted (**7c**), the second cyclization faces difficulties and the oxazolidinedione **8c** is obtained (16%) together with **9c** (56%). When ring A is not activated (**7d**), the yield of the corresponding homoprotoberberine, **9d**, drops to the 23%, the benzylidene isoquinoline **10** being the second reaction product isolated.

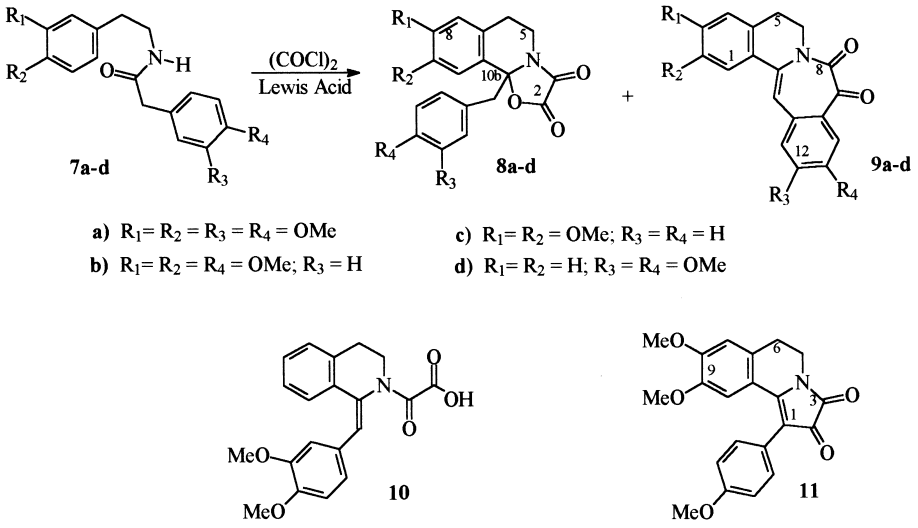
Under these conditions (60°C) and with $SnCl_4$ as Lewis acid, the reaction of amide **7a** afforded a quantitative yield of a crystalline precipitate that was characterized as a complex of the homoprotoberberine retaining one molecule of catalyst (**9a·SnCl$_2$**). An XPS study revealed the presence of Sn(IV), and a 1:1:2 proportion of N/Sn/Cl, and suggested that the metal must be coordinated to the carbonyls of the α-oxoamide functionality. The complex was exhaustively treated with diluted NaOH to remove the metal, and **9a** was obtained in a 29% yield. Similar results were achieved with $TiCl_4$, the complex **9a·TiCl$_2$** being isolated and identified (XPS).

In the reaction of **7b** with $SnCl_4$, the second cyclization is slower and the oxazolidine dione **8b** and the pyrazoloisoquinoline dione **11** are isolated in low yields, in addition to the expected complex (**9b·SnCl$_2$**).

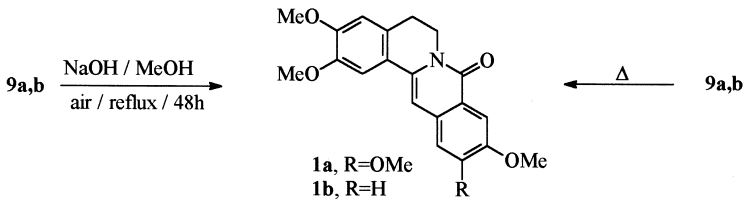
Decarbonylation of **9a** was accomplished via a benzylic acid type rearrangement[20] followed by oxidative decarboxylation, a reaction that has previously been successfully



Scheme 3.



Scheme 4.



Scheme 5.

applied to related α-oxoamides. Thus, treatment of **9a** with NaOH in methanol afforded 8-oxopseudopalmatine (**1a**) (Scheme 5).

Gas evolution was observed on heating over 170°C while the melting point of **9a** was determined. TGA analyses revealed an exothermic peak at 175°C, with a weight lost of about 7% that corresponds to CO elimination. Under these conditions, **9a** was decarbonylated to **1a** (70%). Similar results were obtained for **9b**. On heating this compound at 155°C, 11-demethoxy-8-oxopseudopalmatine (**1b**) was obtained.

The potency of the C-homoprotoberberines (**9a**–**d**) as cytotoxic agents was tested against MDA-MB-231 human breast carcinoma cells. Compounds **9a** and **9c** exhibited significant activity (IC_{50}: 5.2 and 6.2 μg/mL, respectively; 48 h treatment),[21] while **1a** was found to be inactive. The consistent cytotoxicity found for the C-homoprotoberberines and related dioxoisoquinolines suggests that they may function as antineoplastic agents.

Experimental

General methods

The melting points were determined on a Gallenkamp instrument and are given uncorrected. UV spectra were recorded on a Hewlett–Packard 8452A spectrophotometer and IR spectra on a Perkin–Elmer 883 spectrophotometer. Mass spectra were recorded on a HP-MS 5988A spectrometer operating at 70 eV. NMR spectra were obtained on a Bruker WP-200 SY instrument at 200 MHz for ^1H and 50.3 MHz for ^{13}C. ^1H Chemical shifts (δ_H) are given relative to residual $CHCl_3$ (δ_H 7.24 ppm) in deuteriochloroform or to residual CHD_2SOCD_3 in DMSO-d_6 (δ_H 2.50 ppm). *J* values are in Hertz. ^{13}C Chemical shifts (δ_C) are given relative to $CDCl_3$ (δ_C 77.0 ppm) in deuteriochloroform or CD_3SOCD_3 (δ_C 39.7 ppm) in DMSO-d_6. X-Ray Photoelectron Spectra (XPS) were obtained using a Physical Electronics PHI 5700 spectrometer, and TGA analyses were conducted on a Rigaku-Termoflex apparatus. TLC analyses were performed on silica gel 60 F 256 plates, and column chromatography was carried out on silica gel 60 (70–230 mesh). Amides **7a**–**d** were prepared by condensation of phenylethyl amine and homoveratrylamine with the corresponding phenylacetic acids.

Reaction of amides 7a–d with $(COCl)_2/BF_3{\cdot}OEt_2$. General procedure

To a degassed (Ar) solution of the amide **7a**–**d** (2.6 mmol) in dry dichloromethane (25 mL), in a septum sealed round bottom flask, oxalyl chloride (6 mL, 26 mmol) was added. The solution was stirred at 20°C for 15 min, followed by addition of $BF_3{\cdot}OEt_2$ (1.37 mL, 13 mmol) via a syringe. The mixture was stirred at 60°C for 24 h, time during which a solid precipitated. The solid was filtered, washed with CH_2Cl_2 and dried to afford the C-homoprotoberberines **9a**–**d**. The filtrates were washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography to give the stated products.

Reaction of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-3,4-dimethoxyphenylacetamide (7a)

The yellow solid (1 g, 98%) was recrystallized from CH_2Cl_2 and identified as **9a**. No additional products were isolated from the filtrates.

2,3,11,12-Tetramethoxy-5,6-dihydroisoquino[1,2-*b*][3]-benzazepine-8,9-dione (9a). Dark yellow plates, mp 168–170°C (CH_2Cl_2) (gas evolution); ν (KBr) cm^{-1} 1639, 1604; λ_{max} (EtOH) nm (log ϵ): 380 (3.26), 340 (3.64), 288 (4.00), 242 (3.67); δ_H (DMSO-d_6) 8.55 (s, 1H, H-1), 7.59 (s, 1H, Ar-H), 7.51 (s, 1H, Ar-H), 7.34 (s, 1H, H-4), 7.04 (s, 1H, H-14), 4.62 (br t, 2H, CH_2N), 4.05 (s, 3H, OCH_3), 4.93 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.12 (br t, 2H, CH_2); δ_C ($CDCl_3$+TFA) 164.5, 159.0 (C=O), 153.8, 152.4, 149.0, 146.9 (*C*–OCH_3), 139.1, 138.3, 129.1, 119.7, 118.7 (C), 119.2, 111.0, 109.0, 105.1, 104.7 (CH), 57.2 (OCH_3), 56.8 (OCH_3), 56.6 (OCH_3), 56.2 (OCH_3), 52.8 (CH_2N), 26.8 (CH_2); *m*/*z* (%) 395 (M^+, 0), 367 (9), 352 (100), 336 (36); *m*/*z* FAB-MS (%) 396 (MH^+, 45); Anal. Calcd for $C_{22}H_{21}NO_6$: C 66.83, H 5.35, N 3.54%, found C 66.68, H 5.33, N 3.82.

Reaction of *N*-[2-(3,4-dimethoxyphenyl)ethyl]4-methoxyphenylacetamide (7b)

The yellow solid (0.61 g, 65%) was identified as **9b**. No additional products were isolated from the filtrates.

2,3,12-Trimethoxy-5,6-dihydroisoquino[1,2-*b*][3]benzazepine-8,9-dione (9b). Bright yellow plates, mp 150–151°C (CH_2Cl_2) (gas evolution); ν (KBr) cm^{-1} 1617, 1522; λ_{max} (EtOH) nm (log ϵ): 406 (3.48), 338 (4.08), 276 sh (4.00), 260 (4.09), 230 (4.10), 206 (4.01); δ_H ($CDCl_3$+CD_3OD) 8.00 (s, 1H, H-1), 7.82 (d, 1H, *J*=8.9 Hz, H-13), 7.62 (d, 1H, *J*=2.2 Hz, H-10), 7.53 (dd, 1H, *J*=8.9, 2.2 Hz, H-12), 7.27 (s, 1H, H-4), 6.78 (s, 1H, H-14), 4.84 (t, 2H, *J*=6.2 Hz, CH_2N), 4.00 (s, 3H, OCH_3), 3.95 (s, 6H, 2×OCH_3), 3.14 (t, 2H, *J*=6.2 Hz, CH_2); δ_C ($CDCl_3$+CD_3OD) 162.7, 160.5 (C=O), 158.5, 151.9, 149.3 (*C*–OCH_3), 136.4, 134.3, 128.0, 124.5, 119.5 (C), 129.9, 128.1, 116.9, 110.5, 107.9, 107.5 (CH), 56.4 (OCH_3), 56.2 (OCH_3), 56.1 (OCH_3), 52.2 (CH_2N), 29.6 (CH_2); *m*/*z* (%) 365 (M^+, 0), 337 (2), 322 (100), *m*/*z* FAB-MS (%) 366 (MH^+, 20); Anal. Calcd for $C_{21}H_{19}NO_5$: C 69.03, H 5.24, N 3.83%, found C 69.10, H 5.25, N 3.90.

Reaction of *N*-[2-(3,4-dimethoxyphenyl)ethyl]phenylacetamide (7c)

The yellow solid (0.49 g, 56%) was identified as **9c**. The residue from the filtrates was purified by column chromatography (SiO_2, CH_2Cl_2/CH_3OH 20:0.2) to obtain **8c** (0.15 g, 16%).

2,3-Dimethoxy-5,6-dihydroisoquino[1,2-*b*][3]benzazepine-8,9-dione (9c). Yellow crystals, mp 260–261°C (EtOH) (gas evolution); ν (KBr) cm^{-1} 1636, 1602; λ_{max} (EtOH) nm (log ϵ): 388 (3.46), 336 (3.95), 270 (3.88), 252 (4.02), 232 (4.07), 210 sh (2.92); δ_H ($CDCl_3$) 8.51 (d, 1H, *J*=8.4 Hz, H-10), 8.06 (s, 1H, H-1), 7.92 (m, 2H, Ar-H), 7.71 (m, 1H, Ar-H), 7.32 (s, 1H, H-4), 6.80 (s, 1H, H-14), 4.88 (t, 2H, *J*=6.3 Hz, CH_2N), 4.01 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.16 (t, 2H, *J*=6.3 Hz, CH_2); δ_C ($CDCl_3$) 162.0, 161.3 (C=O), 152.3, 149.5 (*C*–OCH_3), 138.4, 138.1, 128.4, 123.0, 119.4 (C), 136.1, 131.8, 129.9, 126.5, 116.9, 110.6, 108.2 (CH), 56.5 (OCH_3), 56.2 (OCH_3), 52.1 (CH_2N), 27.1 (CH_2); *m*/*z* (%) 335 (M^+, 0), 307 (1), 292 (25), 276 (12), 212 (39), 170 (100); *m*/*z* FAB-MS (%) 336 (MH^+, 10); Anal. Calcd for $C_{20}H_{17}NO_4$: C 71.63, H 5.11, N 4.18%, found C 72.04, H 5.18, N 4.32.

10b-Benzyl-6,10b-dihydro-8,9-dimethoxy-5*H*-oxazolo-[2,3-*a*]isoquinoline-2,3-dione (8c). White amorphous solid, mp 152–155°C (CH_2Cl_2/CH_3OH) (gas evolution); ν (KBr) cm^{-1} 1807, 1734, 1608; λ_{max} ($CHCl_3$) nm (log ϵ): 286 (3.42), 244 (3.88); δ_H ($CDCl_3$) 7.27 (m, 3H, Ar-H), 7.08 (m, 2H, Ar-H), 6.88 (s, 1H, Ar-H), 6.60 (s, 1H, Ar-H), 4.47 (ddd, 1H, N–*H*CH), 3.87 (s, 6H, 2×OCH_3), 3.6-3.4 (ddd, 1H, *J*=13.5, 6.9, 1.8 Hz, N–HC*H*), 3.45 (d, 1H, *J*=14.6 Hz, α(C*H*), 3.30 (d, 1H, *J*=14.6 Hz, α*H*CH), 3.06–2.82 (m, 2H, CH_2); δ_C ($CDCl_3$) 158.0, 151.9 (C=O), 150.1, 148.2 (*C*–OCH_3), 131.4, 125.5, 124.8 (C), 91.0 (C-1), 130.6 (2), 128.7 (2), 128.0, 110.8, 108.0 (CH), 56.0 (OCH_3), 55.9 (OCH_3), 46.0, 37.3, 27.1 (CH_2); *m*/*z* (%) 353 (M^+, 0.3), 280 (100), 231 (35), 91 (32); Anal. Calcd for $C_{20}H_{19}NO_5$: C 67.98, H 5.42, N 3.96%, found C 67.89, H 5.28, N 3.84.

Reaction of *N*-(2-phenylethyl)-3,4-dimethoxyphenylacetamide (7d)

The yellow solid (0.20 g, 23%) was identified as **9d**. The residue from the filtrates was purified by column chromatography (SiO_2, CH_2Cl_2/CH_3OH 20:0.5) to obtain **10** (0.14 g, 16% yield).

11,12-Dimethoxy-5,6-dihydroisoquino[1,2-*b*][3]benzazepine-8,9-dione (9d). Yellow crystals, mp 179–181°C (CH_2Cl_2) (gas evolution); ν (KBr) cm^{-1} 1645; λ_{max} (EtOH) nm (log ϵ): 398 (2.85), 314 (2.96), 256 (4.01), 206 (3.38); δ_H ($CDCl_3$) 7.69 (s, 1H, H-10), 7.0–7.4 (m, 6H, ArH), 4.66 (br t, 2H, *J*=6.9 Hz, H-6,6′), 4.09 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.21 (br t, 2H, *J*=7.4 Hz, H-5,5′); δ_C ($CDCl_3$) 163.6, 158.8, (C=O), 152.6 152.4, (*C*–OCH_3), 142.1, 140.1, 135.4, 117.8, 107.7 (C), 129.2 (2), 128.7, 127.8 (2), 103.6, 102.4 (CH), 54.2, 35.5 (CH_2), 57.0, 56.5 (OCH_3); *m*/*z* (%) 335 (M^+, 0), 307 (10), 205 (100); *m*/*z* FAB-MS (%) 336 (MH^+, 5); Anal. Calcd for $C_{20}H_{17}NO_4$: C 71.63, H 5.11, N 4.18%, found C 71.69, H 5.04, N 4.57.

2-{1-[(*Z*)-(3,4-Dimethoxyphenyl)methylidene]-3,4-dihydro-2-isoquinolinyl}-2-oxoacetic acid (10). Yellow needles, mp 162–163°C (CH_3OH); ν (KBr) cm^{-1} 3300, 1686, 1685; λ_{max} (EtOH) nm (log ϵ): 398 (3.17), 254 (3.77), 210 (4.05); δ_H ($CDCl_3$) 7.66 (m, 2H), 7.25 (m, 4H), 6.90 (m, 1H), 3.91 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.77 (m, 2H, CH_2N), 2.92 (t, 2H, *J*=8.0 Hz, CH_2Ph); δ_C ($CDCl_3$) 170.8, 167.4 (C=O), 149.2, 148.7 (*C*–OCH_3), 147.3 (C-4a), 137.8 (C-1a), 128.8 (2), 128.6 (2), 126.7, 121.9 (CH), 121.5 (C-1), 111.1, 111.0, (CH), 107.9 (C-1′), 55.8 (OCH_3), 52.8 (OCH_3), 39.3 (C-3), 34.7 (C-4); *m*/*z* (%) 353 (M^+, 100), 338 (1), 249 (17), 234 (12), 205 (54), 178 (14), 177 (67);

Anal. Calcd for $C_{20}H_{19}NO_5$: C 67.98, H 5.42, N 3.96%, found C 67.80, H 5.61, N 3.89.

Reaction of 7a with $(COCl)_2/SnCl_4$ at 20°C

To a degassed (Ar) solution of the amide **7a** (2.6 mmol) in dry dichloromethane (25 mL), in a septum sealed round bottom flask, oxalyl chloride (6 mL, 26 mmol) was added. The solution was stirred at 20°C for 15 min, followed by addition of stannyl chloride (1.5 mL, 13 mmol) via a syringe. The mixture was stirred at 20°C for 24 h. After this period, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and a few drops of 1 M HCl were added to the solution. The dichloromethanic solution was washed with water, dried over $MgSO_4$ and concentrated to dryness. The residue was separated by column chromatography (SiO_2, CH_2Cl_2/CH_3OH 20:0.5) to obtain **8a** (0.57 g, 63%).

10b-(3,4-Dimethoxybenzyl)-8,9-dimethoxy-6,10b-dihydro-5*H*-oxazolo[2,3-*a*]isoquinoline-2,3-dione (8a). White crystals, mp 160–161°C (CH_3OH); ν (KBr) cm^{-1} 1803, 1734; λ_{max} ($CHCl_3$) nm (log ϵ): 284 (3.85), 246 (2.44); δ_H ($CDCl_3$) 6.93 (s, 1H), 6.76 (d, 1H, *J*=8.7 Hz), 6.58 (m, 3H, Ar-H), 4.45 (m, 1H, N–*H*CH), 3.90 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.45 (d, 1H, *J*=14.8 Hz, α*H*CH), 3.23 (d, 1H, *J*=14.8 Hz, αHC*H*), 3.5–3.1 (m, 2H, CH_2), 2.8 (m, 1H, N–HC*H*); δ_C ($CDCl_3$) 158.2, 151.9 (C=O), 150.2, 149.04, 149.01, 148.4 (*C*–OCH_3), 125.7, 124.9, 123.8 (C), 123.0, 113.7, 111.2, 111.0, 108.1 (CH), 91.2 (C-1), 56.2 (OCH_3), 56.0 (2×OCH_3), 55.8 (OCH_3), 45.9, 37.3, 27.2 (CH_2); *m/z* (%) 413 (M^+, 2), 341 (63), 340 (100), 326 (37), 310 (43), 234 (47), 151 (62); Anal. Calcd for $C_{22}H_{23}NO_7 \cdot 1H_2O$: C 61.23, H 5.84, N 3.25%, found C 61.25, H 5.49, N 3.37.

Reaction of amides with $(COCl)_2/SnCl_4$ at 60°C. General procedure

To a degassed (Ar) solution of the amide **7a**–**c** (2.6 mmol) in dry dichloromethane (25 mL), in a septum sealed round bottom flask, oxalyl chloride (6 mL, 26 mmol) was added. The solution was stirred at 20°C for 15 min, and the tin(IV) chloride (1.5 mL, 13 mmol) added via a syringe. The mixture was stirred at 60°C for 24 h, time during which a solid precipitated. The yellow solid was filtered, washed with CH_2Cl_2, treated with 1 M NaOH (25 mL) for 30 min and then filtered again to give **9a**–**c**. The organic phase was washed with water, dried over $MgSO_4$, concentrated in vacuo and separated by column chromatography to obtain the stated products.

Reaction of amide 7a

9a: Yellow solid, 0.3 g, 29%. The yellow solid before treatment with 1 M NaOH was characterized as **9a·$SnCl_2$**: 1.5 g, 99%; mp >300°C. Anal. Calcd for $C_{22}H_{21}NO_6 \cdot SnCl_2$: C 45.13, H 3.62, N 2.39%, found C 45.20, H 3.78, N 2.41.

Reaction of amide 7b

9b: Yellow solid, 0.3 g, 27%. The residue from the filtrates was separated by column chromatography (SiO_2, CH_2Cl_2 and CH_2Cl_2/CH_3OH 20:0.5) to obtain a 1:1 mixture of **8b** and **11**. The solid mixture was crystallized from CH_2Cl_2/CH_3OH, the crystals were washed several times with methanol to obtain pure **8b** (0.09 g, 9%), and the mother liquor was used to isolate **11** (0.09 g, 10%) by recrystallization from CH_3OH.

10b-(4-Methoxybenzyl)-8,9-dimethoxy-6,10b-dihydro-5*H*-oxazolo[2,3-*a*]isoquinoline-2,3-dione (8b). Colourless needles, mp 147–150°C ($CHCl_3/CH_3OH$) (gas evolution); ν (KBr) cm^{-1} 1801, 1734, 1610; λ_{max} ($CHCl_3$) nm (log ϵ): 284 (3.72), 246 (3.99); δ_H ($CDCl_3$) 7.00 (d, 2H, *J*=8.6 Hz, Ar-H), 6.90 (s, 1H, Ar-H), 6.80 (d, 2H, *J*=8.6 Hz, Ar-H), 6.60 (s, 1H, Ar-H), 4.48 (m, 1H, NCH_2), 3.89 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.45 (d, 1H, *J*=14.8 Hz, α(C*H*), 3.60–3.35 (m, 1H, NCH_2), 3.23 (d, 1H, *J*=14.8 Hz, α*H*CH), 3.2–3.0 (m, 1H, CH_2), 2.70 (m, 1H, CH_2); δ_C ($CDCl_3$) 159.4, 158.2 (C=O), 152.0, 150.2, 148.3 (*C*–OCH_3), 125.6, 124.8, 123.2 (C), 91.1 (C-1), 131.8 (2), 114.2 (2), 110.9, 108.1 (CH), 56.1 (OCH_3), 56.0 (OCH_3), 55.2 (OCH_3), 45.4, 37.3, 27.3 (CH_2); *m/z* (%) 383 (M^+, 1), 310 (100), 280 (41), 234 (29), 121 (78); Anal. Calcd for $C_{21}H_{21}NO_6$: C 65.79, H 5.52, N 3.65%, found C 65.67, H 5.59, N 3.69.

5,6-Dihydro-8,9-dimethoxy-1-(4-methoxyphenyl)-pyrrolo-[2,3-*a*]isoquinoline-2,3-dione (11). Red needles, mp 212–215°C (recrystallized from CH_3OH); ν (KBr) cm^{-1} 1740, 1679; λ_{max} ($CHCl_3$) nm (log ϵ): 512 (3.55), 460 (3.57), 444 (3.58), 380 (3.88), 314 (3.91), 258 (4.07), 246 (4.09); δ_H ($CDCl_3$) 7.26 (d, 2H, *J*=8.7 Hz, Ar-H), 7.03 (s, 1H, Ar-H), 6.92 (d, 2H, *J*=8.7 Hz, Ar-H), 6.73 (s, 1H, Ar-H), 3.9–3.7 (br t, 2H, NCH_2), 3.93 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 3.05 (t, 2H, *J*=6.1 Hz, CH_2); δ_C ($CDCl_3$) 159.3, 158.2 (C=O), 156.7, 153.3, 147.8 (*C*–OCH_3), 132.8, 122.3, 116.8, 108.1 (C), 131.3 (2), 114.3 (2), 111.9, 111.1 (CH), 56.2 (OCH_3), 55.4 (2×OCH_3), 36.3 (NCH_2), 28.6 (CH_2); *m/z* (%) 365 (M^+, 53), 336 (100); Anal. Calcd for $C_{21}H_{19}NO_5$: C 69.03, H 5.24, N 3.83%, found C 68.70, H 5.11, N 4.02.

Reaction of amide 7c

9c: Yellow solid, 0.17 g, 21%. From column chromatography (SiO_2, CH_2Cl_2 and CH_2Cl_2/CH_3OH 20:0.5) of the residue from the filtrates **8c** (white solid, 0.39 g, 42%) was obtained.

Decarbonylation of 9a,b

A mixture of **9a**,**b** (0.3 mmol), NaOH (1.5 g) and methanol (40 mL) was refluxed for 48 h. The solvent was removed in vacuo, and the reaction crude was acidified with concentrated HCl (pH 5). The mixture was diluted with water (15 mL) and extracted with chloroform (2×25 mL). The organic layer was washed with water (15 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, CH_2Cl_2) to give **1a**,**b**.

8-Oxopseudopalmatine (1a). Orange-yellow solid, yield: 0.06 g, 66%; mp 185–186°C (CH_3OH) (mp 198–199°C, 187–188°C);[1c] δ_H ($CDCl_3$) 7.79 (s, 1H, Ar-H), 7.23 (s, 1H, Ar-H), 6.93 (s, 1H, Ar-H), 6.82 (s, 1H, Ar-H), 6.73 (s, 1H, Ar-H), 4.35 (t, 2H, *J*=6.0 Hz, NCH_2), 3.97 (s, 6H,

2×OCH_3), 3.93 (s, 6H, 2×OCH_3), 2.93 (t, 2H, J=6.0 Hz, CH_2); δ_C ($CDCl_3$) 161.3 (C=O), 153.4, 150.0, 148.9, 148.4 (C–OCH_3), 136.1, 132.1, 128.3, 122.4, 118.5 (C), 110.5, 107.8, 107.6, 105.9, 101.0 (CH), 56.1 (2×OCH_3), 56.0 (2×OCH_3), 39.7 (NCH_2), 28.1 (CH_2); *m*/*z* (%) 367 (M^+, 100), 352 (60). This compound (**1a**) was found to be identical (TLC, MS, ^1H and ^{13}C NMR) with an authentic sample obtained by $K_3[Fe(CN)_6]$ oxidation of synthetic pseudopalmatine chloride.[1b]

2,3,10-Trimethoxy-5,6-dihydro-8*H*-isoquino[3,2-*a*]isoquinolin-8-one (1b). Yellowish syrup, 0.05 g, 50%; ν (NaCl) cm^{-1} 1685; λ_{max} ($CHCl_3$) nm (log ϵ): 378 sh (3.69), 362 sh (3.90), 340 (4.11), 246 (3.97); δ_H ($CDCl_3$) 7.81 (d, 1H, J=2.6 Hz, H-9), 7.48 (d, 1H, J=8.7 Hz, H-12), 7.26–7.21 (m, 2H, Ar-H), 6.85 (s, 1H, Ar-H), 6.73 (s, 1H, Ar-H), 4.36 (t, 2H, J=6.2 Hz, NCH_2), 3.97 (s, 3H, OCH_3), 3.92 (s, 6H, 2×OCH_3), 2.93 (t, 2H, J=6.1 Hz, CH_2); δ_C ($CDCl_3$) 161.8 (C=O), 158.4 (C-10), 150.1, 148.5 (C-2, C-3), 135.3, 130.9, 128.3, 125.7, 122.6 (C), 127.6, 123.1, 110.5, 107.70, 107.66, 101.4 (CH), 56.3 (OCH_3), 56.0 (OCH_3), 55.7 (OCH_3), 39.9 (NCH_2), 28.1 (CH_2); *m*/*z* (%) 337 (M^+, 100), 322 (60); Anal. Calcd for $C_{20}H_{19}NO_4$: C 71.20, H 5.68, N 4.15%, found C 71.00, H 5.62, N 4.02.

Thermal decarbonylation of 9a,b

The net products **9a**,**b** (1 mmol) were heated at 175 and 160°C, respectively, until gas evolution ceased (ca. 1 h). After this period, the reaction was cooled and the crude residue was separated by column chromatography (SiO_2, CH_2Cl_2) to obtain **1a**,**b** in 70 and 36% yield, respectively.

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