Synthesis of 3,4-Dioxocularine and Aristocularine Alkaloids in a Convergent Route from Aryloxy-phenyl Acetamides Involving Oxalyl Chloride-Lewis Acid

Rafael Suau,* Rodrigo Rico, Juan Manuel López-Romero, Francisco Nájera, Antonio Ruiz and Francisco Javier Ortiz-López

Departamento de Química Orgánica. Universidad de Málaga. E 29071-Málaga. Spain
E-mail : suau@uma.es

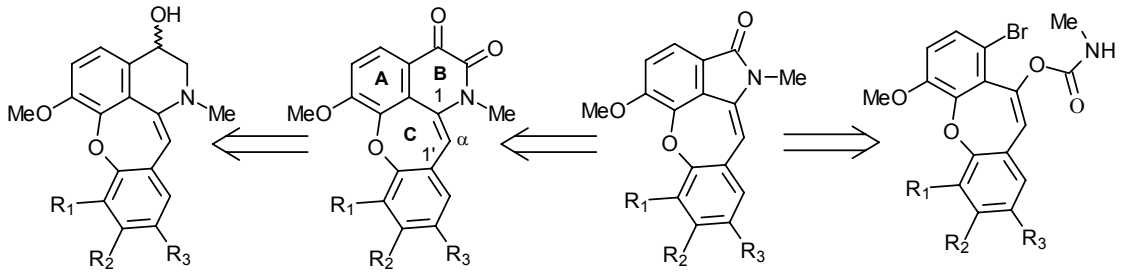
Dedicated to Professor Marcial Moreno-Mañas on the occasion of his 60th birthday

Abstract
Double cyclization of aryloxy-phenyl acetamides is promoted by oxalyl chloride/stannyl chloride and gives 3,4-dioxocularine and aristocularine alkaloids. Rearrangement of the dibenzoxepine ring prior to the second cyclization produces xanthene derivatives. The synthesized cularinoids exhibit significant activity against various tumoral cell lines.

Keywords: Aryloxyphenyl acetamides, 3,4-dioxocularine, aristocularine, alkaloids, double cyclization

Introduction

Cularinoids are a group of isoquinoline alkaloids consisting of about sixty members that are characterized by the dibenzoxepine skeleton and occur naturally in various oxidation states. Among them, 3,4-dioxocularines and aristocularines are oxidized cularinoids characterized by the tetracyclic structure **1** and **2**, respectively.[1] Partial synthesis of 3,4-dioxocularines has been accomplished by chemical oxidation of 4-hydroxycularines with DDQ.[2a-c] Aristocularines are prepared by benzylic type rearrangement of 3,4-dioxocularines and decarbonylation in an alkaline medium.[2b] Aristoyagonine 2 was the first five-membered lactam derivative isolated from natural sources.[2e] A partial synthesis for this alkaloid involving a multistep sequence from 4-hydroxysarcocapnine has been reported.[2b] Its total synthesis has been achieved by annelation of metallated bromo-dibenzoxepine (Scheme 1).[2c]



1
R_1=R_2=OMe, R_3=H,
4-Hydroxysarcocapnine

2
R_1=R_2=OMe, R_3=H,
Aristoyagonine

Scheme 1
Synthetic pathways to 3,4-dioxocularine and aristocularine alkaloids.

A few years ago, we developed new approaches to the synthesis of 4,5-dioxoaporphines from preformed biaryl bond precursors.[3] We found biarylacetamides[4] to undergo a cascade reaction including a double cyclization induced by oxalyl choride/Lewis acid. Extension of this double cyclization to phenylethyl phenylacetamides provided a much simpler way to access C-homoberbines and protoberberine alkaloids.[5]

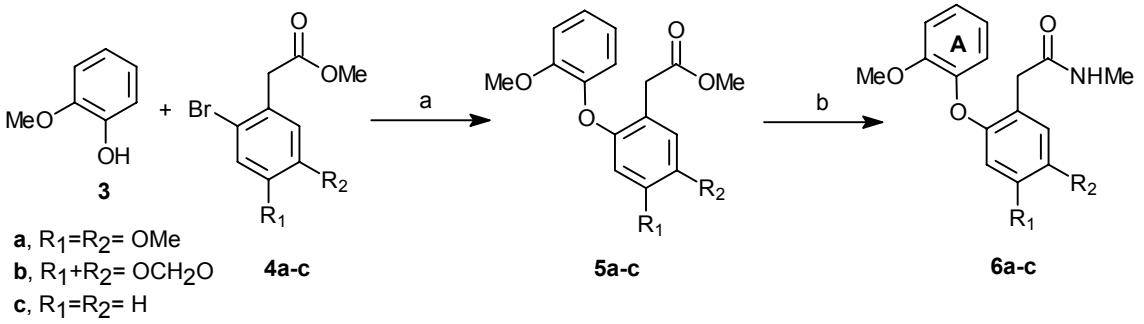
Based on this approach, in this work we examined the reaction of aryloxy-phenyl acetamides with oxalyl chloride-Lewis acid to promote a double cyclization with a view to obtaining various 3,4-dioxocularines and aristocularines.[6]

Results and Discussion

The reactivity of oxalyl chloride with amides has been studied by Speziale.[7] Oxalyl chloride is known to react with secondary amides to give the 2-chloro-oxazolidine-4,5-dione ring.[7c] The addition of Lewis acids to these halogenated heterocycles derived from phenethylamides yields N-acyliminium ions; these act as superior acylating agents in the synthesis of isoquinolines.[8]

We designed the synthesis of 3,4-dioxocularines in two stages. First, Ullmann condensation would allow easy access to the aryloxy-phenyl acetamides, as starting products, and then, activation of these amides with oxalyl chloride/Lewis acid would induce double cyclization and the sequential formation of rings C and B in the cularine skeleton. The presence of two oxygenated substituents at ring A in the starting acetamide **6a-c** ensures appropriate activation of the aromatic system, which must compensate for the formation of the seven-member dibenzoxepine ring in the first cyclization.

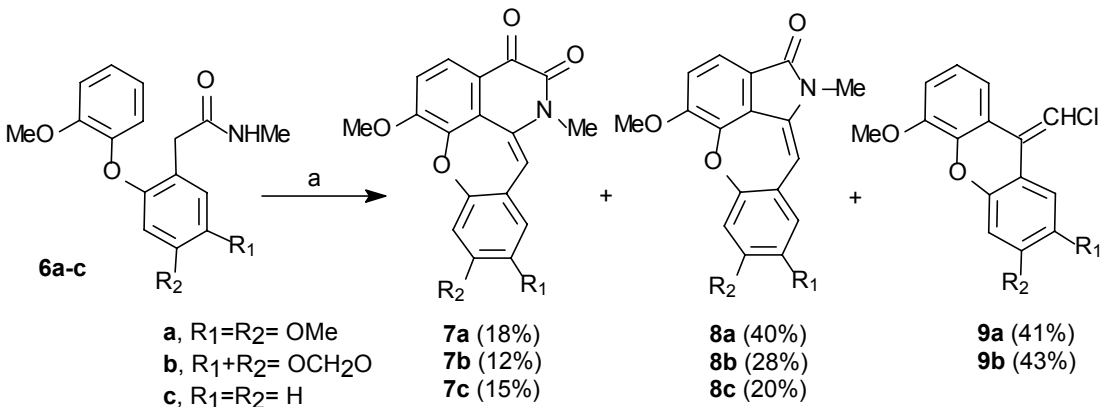
Starting products **6a-c** were prepared by classical Ullmann condensation of guaiacol 3 with the bromo-phenylacetates **4a-c**.[9] Efficient aminolysis of the ester group gave the aryloxy-phenyl acetamides **6a-c** (Scheme 2).[10] Compound **6b** was also prepared in good yield by direct Ullmann condensation of guaiacol and 2-bromo-3,4-methylenedioxy-phenyl N-methylacetamide.



Scheme 2

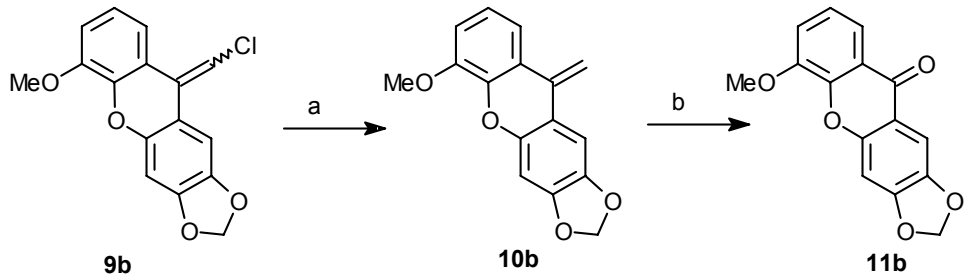
(a) Cu/CuO//Py, reflux, 36h; (b) $MeNH_2$/NaCN/MeOH, 60 ºC, 2 h.

The reaction of the amide **6a,b** with oxalyl chloride and stannyl chloride was carried out at 70 ºC (Scheme 3). Under these conditions, three reaction products were obtained that were characterized from their spectroscopic properties as the 3,4-dioxocularines **7a,b**, the aristocularines **8a,b**, and the chloro-xanthene derivatives **9a,b**. The structures of dioxocularine **7a** and aristocularine **8a** were also identified by comparison with authentic samples.[11,12]



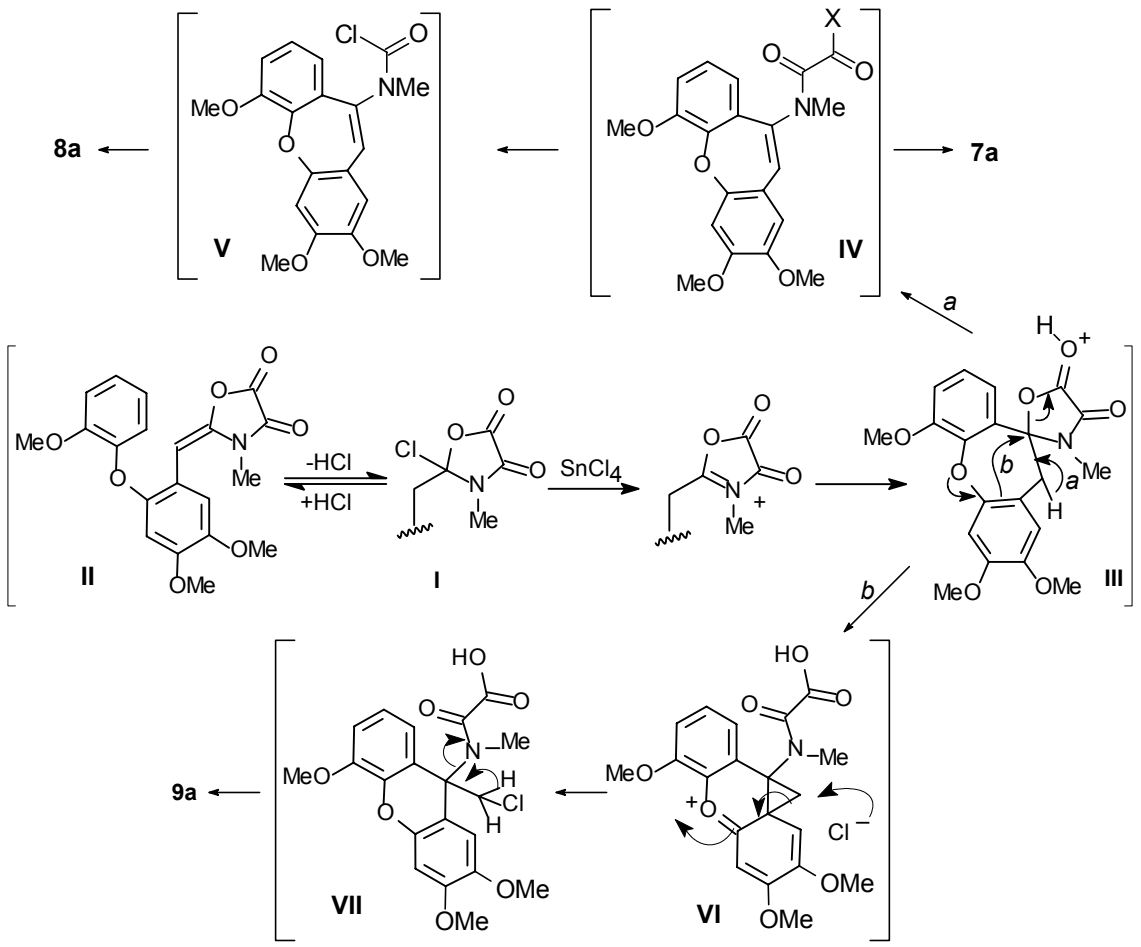
Scheme 3
(a) 1) $(COCl)_2/CH_2Cl_2$; 2) $SnCl_4/CH_2Cl_2$.

Further proof of the structure of **9b** was obtained chemically. Thus, treatment of the isomeric mixture of both *Z*/*E* **9b** with magnesium in THF, followed by careful addition of humid THF, led to the reduction of the vinyl chloride to afford **10b** as a single product (Scheme 4). This methylene derivative was oxidized by air to the corresponding xanthone **11b**.



Scheme 4
(a) Mg/THF; (b) O_2.

The mechanism of the reaction involves (Scheme 5) firstly the 2-chloro-oxazolidine-4,5-dione **I**, formed by reaction of the amide with oxalyl chloride. This intermediate, **I**, is in equilibrium with the 2-methylene-oxazolidine-4,5-dione **II**, as found by ^{1}H-NMR. In fact, when a dichloromethane solution of compound 6a was treated with excess oxalyl chloride for 10 min at room temperature, and the solvent and excess reagent were removed under vacuum, the alkylidene derivative **II** was obtained in virtually quantitative yield (see experimental part). When stannyl chloride was added over **I**⇔**II**, the *N*-acyliminium ion must be formed, and the electrophilic substitution led to the spiro-oxazolidinedione intermediate **III**. Opening of the spiro intermediate **III** (*path a*) in a, probably, HCl-catalyzed reaction, would give the dibenzoxepine-oxalylamide derivative (**IV**, X = OH)[13], which should react with excess oxalyl chloride to give the corresponding acid chloride (**IV**, X = Cl). A Friedel-Craft reaction catalyzed by stannyl chloride accounts for the formation of the dioxocularine **7a**.



Scheme 5

Cyclization of amides with oxalyl chloride and stannyl chloride.

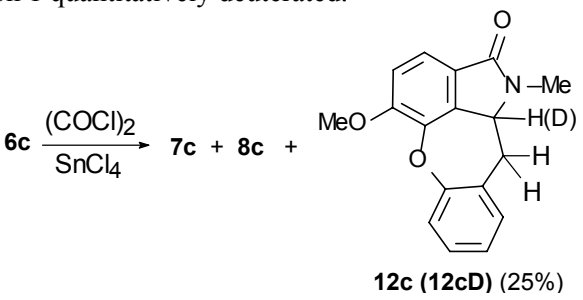
Initially, we suspected that the formation of the aristocularine **8a** was due to ring B decarbonylation of dioxocularine **7a**.[14,2b] However, when dioxocularine **7a** was subjected to the reaction conditions [$(COCl)_2$/$SnCl_4$/70 ºC] for 5 h, no decarbonylation product such as **8a** was detected. Therefore, we assume that the formation of aristocularine **8a** should be due to decarbonylation of the oxalylamide intermediate **IV** to the monocarbonyl derivative **V**, with final acylation to the aristocularine **8a**. The formation of phosgene in the mixture of oxalyl chloride with Lewis acids is not without precedent.[15]

We hypothesize that xanthene derivative **9a** is formed by ring-C contraction of the dibenzoxepine from the common intermediate **III** (*path b*) leading to the cyclopropane intermediate **VI**. The attack of chloride ion on the cyclopropane intermediate and elimination of the oxalylamide residue from intermediate **VII** should generate the exocyclic double bond of **9a**. This rearrangement has been observed in dibenzoxepinones in acidic media,[16] and has been investigated in order to use this reaction as the key step in the synthesis of clavizepine[17] (Scheme 5).

The reaction of **6c** with oxalyl chloride and stannyl chloride was carried out under similar conditions to those described previously (Scheme 6). The reaction was showed to introduce significant differences. From silica gel column chromatography of the reaction mixture, the

expected 3,4-dioxocularine **7c** and aristocularine **8c** were isolated, together with the unexpected dihydroaristocularine **12c**.

Compound **12c** exhibits the characteristic ^{1}H-NMR spectrum for reduced cularine alkaloids, with an ABX system at 4.50 ppm (dd, J = 11.3, 2.7 Hz), 3.41 ppm (dd, J = 13.6 and 2.7 Hz) and 2.87 ppm (bt) corresponding to the protons at positions 1 and α. The formation of this product might be related to the non-oxidative decarbonylation of the oxalylamide intermediate **IV** (Scheme 5). What we know, so far, is that the proton at position 1 comes from the quenching of the reaction with water. In fact, when the reaction mixture was treated with D_2O, product **12cD** was isolated with position 1 quantitatively deuterated.



Scheme 6
Reaction of the amide **6c**.

When the reaction of amide **6a** was carried out at a lower temperature (5 ºC), a higher percentage of xanthene derivative **9a** was obtained together with unreacted amide. Changing the solvent from methylene chloride to carbon disulfide decreased the reaction rate and the yield of cyclization products. With other Lewis acids such as $BF_3{\cdot}OEt_2$, titanium tetrachloride, iron trichloride or aluminum chloride, no cyclization products were obtained as inferred from the ^{1}H-NMR spectrum for the reaction crude.

The cytotoxicity of cularinoids was also analyzed. The results are shown in Table 1.[18] The potency of these cularinoids as cytotoxic agents varied among cell lines. The compounds exhibited significant activity against both wild-type and adriamycin-resistant P-388 cell lines, and were also active against H-29 human colon adenocarcinoma and MDA-MB-231 human breast carcinoma cells. The IC_{50} values obtained are consistent with those reported for aporphine alkaloids[3,19] and suggest that cularinoids may function as antineoplastic agents.

Table 1. Cytotoxicity data, IC_{50} (μg/mL), treatment for 48 h.

Compound	Cell Line			
	MDA	**HT-29**	**P-388**	**SCHABEL**
3,4-Dioxocularines				
7a, Dioxocularine	3.7	8.5	1.0	2.3
7b	5.0	6.0	2.6	3.0
7c	7.3	5.9	2.6	3.0
Aristocularines				
8a, Aristocularine	2.9	7.5	<0.8	<0.9
8b	7.2	4.7	2.5	2.6
8c	6.8	5.0	2.8	2.8
12c	4.7	5.0	3.6	3.3

In conclusion, a new, short synthesis of oxidized cularinoids based on the cyclization of aryloxy-phenyl acetamides to build up the rings B and C in a cascade reaction promoted by oxalyl chloride and stannyl chloride was developed. The reaction exhibits major differences with those reported for the formation of 4,5-dioxoaporphines,[4] where no aristolactams are formed and, consequently, yields for dioxoaporphines are much higher. Probably, the second cyclization and ring B formation are facilitated in aporphine by the rigidity of the phenanthrene structure. The flexibility of the dibenzoxepine skeleton may hinder cyclization, thus favoring the competitive decarbonylation process.

Experimental

General. Melting points (uncorrected) were determined on a Gallenkamp instrument. UV-spectra were recorded on a Hewlett-Packard 8452A spectrophotometer and IR-spectra on a Perkin-Elmer 883 spectrophotometer. Low- and high-resolution mass spectra were recorded on a HP-MS 5988A and a Kratos MS 50 spectrometer, respectively, both operating at 70 eV. ^{1}H- and ^{13}C-NMR spectra were obtained on Bruker WP-200 SY instrument, at 200 MHz for ^{1}H and 50.3 MHz for ^{13}C. ^{1}H Chemical shifts are given relative to residual $CHCl_3$ (δ_H 7.24 ppm) in deuteriochloroform. Coupling constants, *J*, value are given in Hz. ^{13}C Chemical shifts are given relative to $CDCl_3$ (δ_C 77.0 ppm) in deuteriochloroform. Analytical TLC was performed on silica gel 60 F_{256} (Merck) plates and visualized by UV light. Column chromatography (cc) was carried out on silica gel 60 (70-230 mesh).

Ullmann condensation of the methyl esters 4a-c. Synthesis of esters 5a-c.

General procedure: A mixture of **4a-c** (20 mmol), guaiacol 3 (5.0 g, 40 mmol), copper (0.6 g), copper oxide (4 g), potassium carbonate (5.6 g) and pyridine (30 mL) was refluxed for 36 h under an Ar atmosphere. The cooled reaction mixture was filtered over celite and thoroughly washed with dichloromethane. The filtrates were washed with 1 M hydrochloric acid, 1 M sodium hydroxide and water, dried over anhydrous $MgSO_4$ and concentrated to dryness to give the title compounds **5a-c**.

Methyl 2-(2'-methoxyphenoxy)-4,5-dimethoxy-phenylacetate 5a. Colorless syrup, 4.98 g, 75%; ^{1}H-NMR δ ($CDCl_3$) 7.04-6.64 (5H, m, Ar-H), 6.46 (1H, s, Ar-H), 3.88 (3H, s, OMe), 3.86 (3H, s, OMe), 3.72 (3H, s, OMe), 3.60 (2H, s, CH_2), 3.57 (3H, s, OMe); ^{13}C-NMR δ ($CDCl_3$) 172.0 (CO), 149.9, 148.9, 147.8, 147.1, 145.4 (C), 117.2 (C-1), 123.1, 120.8, 117.4, 113.4, 112.4, 104.1 (CH), 56.2, 56.0, 56.0, 51.9 (4xOMe), 34.8 (CH_2); *m/z* (%) 332 (M^+, 100), 317 (19), 273 (41); IR ν 1738 cm^{-1}; Anal. Calcd. for $C_{18}H_{20}O_6$: C 65.05, H 6.06, found C 65.28, H 6.00.

Methyl 2-(2'-methoxyphenoxy)-4,5-methylenedioxy-phenylacetate 5b. White solid, 4.55 g, 72%; mp 79-81 ºC; ^{1}H-NMR δ ($CDCl_3$) 7.1-6.7 (4H, m, Ar-H), 6.74 (1H, s, Ar-H), 6.36 (1H, s, Ar-H), 5.89 (2H, s, OCH_2O), 3.84 (3H, s, OMe), 3.61 (2H, s, CH_2), 3.59 (3H, s, OMe); ^{13}C-NMR δ ($CDCl_3$) 171.9 (CO), 150.5, 149.5, 147.3, 146.4, 143.3 (C), 117.5 (C-1), 123.9, 120.9, 118.9, 112.5, 110.0, 100.6 (CH), 101.4 (OCH_2O), 55.9, 51.5 (2xOMe), 35.0 (CH_2); *m/z* (%) 316 (M^+, 100), 257 (52), 151 (91); IR ν 1735 cm^{-1}; Anal. Calcd. for $C_{17}H_{16}O_6$: C 64.55, H 5.10, found C 64.74, H 5.05.

Methyl 2-(2'-methoxyphenoxy)phenylacetate 5c. Syrup, 3.64 g, 67%; ^{1}H-NMR δ ($CDCl_3$) 7.30-6.86 (7H, m, Ar-H), 6.70 (1H, m, Ar-H), 3.81 (3H, s, OMe), 3.77 (2H, s, CH_2), 3.63 (3H, s, OMe); ^{13}C-NMR δ ($CDCl_3$) 171.9 (CO), 155.8, 151.5, 145.3 (C), 124.6 (C-1), 131.1, 128.4, 124.5, 122.7, 121.0, 120.6, 116.7, 112.7 (CH), 55.9, 51.8 (2xOMe), 35.6 (CH_2); *m/z* (%) 272

(M^+, 100), 213 (69), 197 (37), 181 (81); IR ν 1739 cm^{-1}; Anal. Calcd. for $C_{16}H_{16}O_4$ 1/2 H_2O: C 68.32, H 6.09, found C 68.38, H 6.25.

Aminolysis of esters 5a-c. Synthesis of amides 6a-c.[9]

General procedure: A solution of **5a-c** (12.0 mmol), sodium cyanide (0.058 g, 1.2 mmol) and methylamine (50 mL, 580 mmol) in methanol (100 mL) in a sealed round bottom flask was stirred at 60 ºC (bath temperature). After 2 h, the methanol was removed in vacuo and the residue was dissolved in dichloromethane. This solution was washed with water, dried and evaporated to dryness to obtain **6a-c**.

2-(2'-Methoxyphenoxy)-4,5-dimethoxy-N-methyl-phenylacetamide 6a. White solid, 3.42 g, 86%; mp 97-8 ºC (EtOH); ^{1}H-NMR δ ($CDCl_3$) 7.09-6.75 (5H, m, Ar-H), 6.40 (1H, s, Ar-H), 6.32 (1H, brs, N<u>H</u>CH_3), 3.84 (3H, s, OMe), 3.82 (3H, s, OMe), 3.68 (3H, s, OMe), 3.44 (2H, s, CH_2CO), 2.69 (3H, d, J=4.9, NH<u>Me</u>); ^{13}C-NMR δ ($CDCl_3$) 171.6 (CO), 149.9, 148.7, 147.5, 145.5, 145.3 (C), 117.3 (C-1), 124.0, 121.0, 118.2, 113.5, 112.3, 102.8 (CH), 56.1, 56.0, 55.9 (3xOMe), 38.1 (CH_2), 26.4 (NHMe); *m/z* (%) 331 (M^+, 89), 273 (62), 167 (100); IR ν 3324, 1646 cm^{-1}; Anal. Calcd. for $C_{18}H_{21}NO_6$: C 65.24, H 6.39, N 4.23, found C 65.15, H 6.41, N 4.13.

2-(2'-Methoxyphenoxy)-4,5-methylenedioxy-N-methyl-phenylacetamide 6b.
White solid, 3.48 g, 92%; mp 125-7 ºC (MeOH); ^{1}H-NMR δ ($CDCl_3$) 7.13-6.81 (4H, m, Ar-H), 6.77 (1H, s, Ar-H), 6.31 (1H, brs, N<u>H</u>Me), 6.30 (1H, s, Ar-H), 5.87 (2H, s, OCH_2O), 3.81 (3H, s, OMe), 3.46 (2H, s, CH_2CO), 2.70 (3H, s, NH<u>Me</u>); ^{13}C-NMR δ ($CDCl_3$) 171.6 (CO), 150.4, 149.2, 147.2, 144.8, 143.3 (C), 117.7 (C-1), 124.6, 121.1, 119.6, 112.5, 110.3, 99.3 (CH), 101.4 (OCH_2O), 55.9 (OMe), 35.2 (CH_2), 26.4 (NHMe); *m/z* (%) 315 (M^+, 90), 257 (54), 151 (100); IR ν 3428, 1649 cm^{-1}; Anal. Calcd. for $C_{17}H_{17}NO_5$: C 64.75, H 5.43, N 4.44, found C 64.56, H 5.40, 4.36.

2-(2'-Methoxyphenoxy)-N-methyl-phenylacetamide 6c. White solid, 3.02 g, 93%; mp 83-4ºC (MeOH); ^{1}H-NMR δ ($CDCl_3$) 7.30-6.90 (7H, m, Ar-H), 6.60 (1H, dd, J=8.0 and 1.0, Ar-H), 6.49 (1H, brs, N<u>H</u>Me), 3.76 (3H, s, OMe), 3.64 (2H, s, CH_2), 2.70 (3H, d, J=4.9, NHMe); ^{13}C-NMR δ ($CDCl_3$) 171.4 (CO), 155.3, 150.9, 143.5 (C), 124.6 (C-1), 131.3, 128.3, 125.3, 122.7, 121.2, 121.2, 115.0, 112.5 (CH), 55.8 (OMe), 38.5 (CH_2), 26.3 (NHMe); *m/z* (%) 271 (M^+, 100), 240 (19), 214 (75), 181 (80); IR ν 3261, 1644 cm^{-1}; Anal. Calcd. for $C_{16}H_{17}NO_3$: C 70.83, H 6.31, N 5.16, found C 70.78, H 6.26, N 5.05.

Reaction of 6a with $(COCl)_2$

An Ar degassed solution of 6a (0.022 g, 0.08 mmol) in dry CD_2Cl_2 (1 mL) was cooled at 0ºC and oxalyl chloride (38 μL, 0.40 mmol) was added. After 2 min the ^{1}H-NMR spectrum shows the intermediate **I** with a small quantity of **II**. After 10 min at room temperature the solvent and the excess of reagent were removed under vacuum to obtain the alkylidene derivative **II**.

I. ^{1}H-NMR δ (CD_2Cl_2) 7.15-6.80 (4H, m, Ar-H), 6.75 (1H, s, Ar-H), 6.23 (1H, s, Ar-H), 4.05 (1H, d, J=16.0, CH_2CClO), 3.78 (3H, s, OMe), 3.76 (3H, s, OMe), 3.62 (1H, d, J=16.0, CH_2CClO), 3.61 (3H, s, OMe), 3.26 (3H, s, NH<u>Me</u>).

II. Yellow solid, 0.030 g, mp 206-8ºC ($CHCl_3$/MeOH); ^{1}H-NMR δ ($CDCl_3$) 7.40 (1H, s, CH), 7.06-6.96 (2H, m, Ar-H), 6.85 (1H, t, J=8, Ar-H), 6.72 (1H, d, J=8, Ar-H), 6.43 (1H, s, Ar-H), 5.79 (1H, s, Ar-H), 3.90 (3H, s, OMe), 3.88 (3H, s, OMe), 3.73 (3H, s, OMe), 3.25 (3H, s,

NHMe); ^{13}C-NMR δ ($CDCl_3$) 154.5, 150.1, 149.7, 149.3, 148.5, 146.6, 145.6, 140.2, 124.0, 121.1, 118.3, 114.9 (C), 112.5, 111.3, 103.3, 85.5, 56.3 (OMe), 56.0 (2xOMe), 27.3 (NMe); *m/z* (%) 385 (M^+, 80), 300 (49), 241 (100); IR ν 1808, 1686 cm^{-1}; UV (EtOH) (log ε) 384 (3.83), 254 (3.95) nm; Anal. Calcd. for $C_{20}H_{19}NO_7$ 1/2 H_2O: C 60.91, H 5.11, N 3.55, found C 61.26, H 5.11, N 3.55.

Reaction of 6a-c with $(COCl)_2/SnCl_4$.

General procedure: Over an Ar degassed solution of **6a-c** (2 mmol) in dry dichloromethane (30 mL), oxalyl chloride (1.5 mL, 16 mmol) was added. The flask was sealed (septum) and heated at 70 ºC, and stannyl chloride (1.4 mL, 11.3 mmol) was added. The reaction mixture was stirred at 20 ºC for 5 h. After this period, it was diluted with dichloromethane and 2 M hydrochloric acid was added. The dichloromethane was separated and washed with 2 M hydrochloric acid and water. The organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. The residue was separated by cc (CH_2Cl_2/MeOH, 100:0-100:2-100:15).

Dioxocularine 7a. Red crystals, 0.13 g, 18%; mp 214-8 ºC ($CHCl_3$); [Lit.[11] 212-214 (EtOH)]; ^{1}H-NMR δ ($CDCl_3$) 8.03 (1H, d, J=8.8, H-5), 7.18 (1H, d, J=8.8, H-6), 6.90 (1H, s, H-5'), 6.67 (1H, s, H-2'), 6.62 (1H, s, H-α), 4.05 (3H, s, OMe), 3.92 (3H, s, OMe), 3.84 (3H, s, OMe), 3.66 (3H, s, NMe); ^{13}C-NMR δ ($CDCl_3$) 175.2 (C-4), 156.7 (C-3, C-7), 151.1, 148.7, 146.6 (C-3', C-4', C-6'), 141.2 (C-8), 134.2 (C-1), 129.5, 121.7, 119.8 (C), 126.8, 118.1, 113.8, 111.1 (CH), 105.0 (C-α), 56.6, 56.3, 56.3 (3xOMe), 33.0 (NMe); *m/z* (%) 367 (M^+, 100), 339 (23), 324 (34); IR ν 1686, 1666 cm^{-1}; UV (EtOH) (log ε) 438 (3.48), 336 (3.73), 296 (3.65), 252 (3.83), 212 (4.20) nm.

Aristocularine 8a. Red amorphous solid, 0.27 g, 40%; mp 180-3 ºC [Lit.[12] 187-9 ºC]; ^{1}H-NMR δ ($CDCl_3$) 7.30 (1H, d, J=8.3, Ar-H), 6.90 (1H, d, J=8.3, Ar-H), 6.57 (1H, s, Ar-H), 6.41 (1H, s, Ar-H), 5.65 (1H, s, H-α), 3.91 (3H, s, OMe), 3.86 (3H, s, OMe), 3.82 (3H, s, OMe), 3.21 (3H, s, NMe); ^{13}C-NMR δ ($CDCl_3$) 166.0 (CO), 151.5, 149.6, 147.1, 145.7, 141.7 (C-3', C-4', C-6, C-6', C-7), 136.4 (C-1), 127.4, 122.0, 118.9 (C), 118.5, 114.6, 113.5, 107.7 (CH), 106.6 (C-α), 56.5, 56.2, 56.1 (3xOMe), 25.6 (NMe); *m/z* (%) 339 (M^+, 100), 324 (34), 296 (28); IR ν 1692, 1668 cm^{-1}; UV (EtOH) (log ε) 410 (3.09), 282 (3.71), 206 (4.15) nm.

2,3,5-Trimethoxy-9-methylenechloroxanthene 9a. Brown solid, 0.26 g, 41%; mp 116-7 ºC ($CHCl_3$, Z:E mixture, 3:1); ^{1}H-NMR δ ($CDCl_3$) Mayor isomer (Z), 7.93 (1H, s, H-1), 7.1-6.7 (4H, m, Ar-H), 6.33 (1H, s, =CHCl), 3.93, 3.90, 3.89 (3x3H, 3xs, 3xOMe); ^{13}C-NMR δ ($CDCl_3$) Mayor isomer (Z), 150.2, 148.1, 146.5, 144.4, 140.3, 126.6, 122.5, 110.9 (C), 123.2, 114.8, 110.6, 109.3, 108.3 (CH), 100.3 (CHCl), 56.2, 56.1, 56.0 (3xOMe); *m/z* (%) 320 (M^+, 33), 318 (100), 303 (20); IR ν 1634 cm^{-1}; Anal. Calcd. for $C_{16}H_{11}NO_4{}^{35}Cl$: C 64.06, H 4.74, found C 64.13, H 4.84.

O-Methyl-3,4-dioxo-dehydrocularicine 7b. Orange solid, 0.084 g, 12%; mp 283-90 ºC ($CHCl_3$); ^{1}H-NMR δ ($CDCl_3$+TFA) 8.09 (1H, d, J=8.8, Ar-H), 7.26 (1H, d, J=8.8, Ar-H), 6.91 (1H, s, Ar-H), 6.80 (1H, s, Ar-H), 6.68 (1H, s, H-α), 6.02 (2H, s, OCH_2O), 4.07 (3H, s, OMe), 3.73 (3H, s, NMe); ^{13}C-NMR δ ($CDCl_3$+TFA) 175.2 (C-4), 158.4, 158.2 (C-3, C-7), 150.9, 149.9, 145.7, 140.2 (C-3', C-4', C-6', C-8), 132.9 (C-1), 129.8, 122.0, 120.2 (C), 128.1, 120.7, 114.6, 108,1 (CH), 103.3 (C-α), 102.5 (OCH_2O), 56.9 (OMe), 33.8 (NMe); *m/z* (%) 351 (M^+, 100), 323 (32); IR ν 1669 cm^{-1}; UV (EtOH) (log ε) 436 (3.45), 326 sh (3.61), 296 (3.74), 266 sh

(3.79), 248 sh (3.88), 206 (4.31) nm; Anal. Calcd. for $C_{19}H_{13}NO_6$: C 64.96, H 3.73, N 3.99, found C 64.33, H 3.44, N 3.95.

O-Methyl-aristocularicine 8b. Yellow needles, 0.18 g, 28%; mp 234-8 ºC dec. ($CHCl_3$); ^{1}H-NMR δ ($CDCl_3$) 7.32 (1H, d, J=8.1, Ar-H), 6.91 (1H, d, J=8.1, Ar-H), 6.59 (1H, s, Ar-H), 6.42 (1H, s, Ar-H), 5.93 (2H, s, OCH_2O), 5.64 (1H, s, H-α), 3.90 (3H, s, OMe), 3.20 (3H, s, NMe); ^{13}C-NMR δ ($CDCl_3$) 166.1 (CO), 151.8, 148.5, 148.1, 144.9, 141.4 (C-3', C-4', C-6, C-6', C-7), 136.5 (C-1), 128.0, 121.8, 120.8 (C), 118.9, 114.9, 109.4, 107.7 (CH), 104.4 (C-α), 101.9 (OCH_2O), 56.6 (OMe), 25.6 (NMe); *m/z* (%) 323 (M^+, 100), 308 (7); IR ν 1705, 1655 cm^{-1}; UV (EtOH) (log ε) 412 (3.27), 286 (3.86), 236 sh (3.89), 208 (4.08) nm; Anal. Calcd. for $C_{18}H_{13}NO_5$: C 66.87, H 4.05, N 4.33, found C 66.90, H 4.20, N 4.36.

2,3-Methylenedioxy-5-methoxy-9-methylenechloroxanthene 9b. Brown solid, 0.26 g, 43%; mp 106-7 ºC ($CHCl_3$, Z:E mixture, 3:2.5); ^{1}H-NMR δ ($CDCl_3$) Mayor isomer (Z), 7.82 (1H, s, H-1), 7.1-6.7 (4H, m, Ar-H), 6.32 (1H, s, =CHCl), 5.96 (2H, d, OCH_2O), 3.89 (3H, s, OMe); ^{13}C-NMR δ ($CDCl_3$) Mayor isomer (Z), 148.0, 147.8, 145.8, 143.2, 140.3, 122.6, 126.9, 112.0 (C), 123.4, 114.7, 110.7, 108.9, 106.0 (CH), 101.6 (OCH_2O), 98.4 (CHCl), 56.0 (OMe); *m/z* (%) 304 (M^+, 33), 302 (100), 287 (47); IR ν 1630 cm^{-1}; UV ($CHCl_3$) (log ε) 342 (3.80), 296 sh (3.43), 268 sh (3.38), 250 (4.00) nm; Anal. Calcd. for $C_{16}H_{11}O_4{}^{35}Cl$: C 63.48, H 3.66, found C 63.56, H 3.73.

3',4'-Demethoxy-dioxocularine 7c. Yellow solid, 0.082 g, 15%; mp 222-6 ºC (CH_2Cl_2); ^{1}H-NMR δ ($CDCl_3$) 8.02 (1H, d, J=8.8, Ar-H), 7.18 (1H, d, J=8.8, Ar-H), 7.36-7.16 (4H, m, Ar-H), 6.68 (1H, s, H-α), 4.04 (3H, s, OMe), 3.66 (3H, s, NMe); ^{13}C-NMR δ ($CDCl_3$) 175.1 (C-4), 157.0, 156.8 (C-3, C-7), 154.9 (C-6'), 141.7 (C-8), 135.5 (C-1), 129.3, 128.3, 121.7 (C), 130.5, 129.9, 126.8, 125.6, 121.4, 117.9, 113.9 (CH), 56.6 (OMe), 32.9 (NMe); *m/z* (%) 307 (M^+, 100), 279 (93), 264 (45); IR ν 1668 cm^{-1}; UV (EtOH) (log ε) 398 sh (3.36), 332 (3.72), 286 sh (3.87), 256 sh (4.00), 216 (4.42) nm; Anal. Calcd. for $C_{18}H_{13}NO_4$: C 70.35, H 4.26, N 4.56, found C 70.30, H 4.30, N 4.60.

4',5'-Demethoxy-aristoyagonine 8c. Yellow needles, 0.11 g, 20%; mp 132-5 ºC ($CHCl_3$); ^{1}H-NMR δ ($CDCl_3$) 7.28 (1H, d, J=8.4, Ar-H), 7.1-6.9 (4H, m, Ar-H), 6.89 (1H, d, J=8.4, Ar-H), 5.70 (1H, s, H-α), 3.89 (3H, s, OMe), 3.20 (3H, s, NMe); ^{13}C-NMR δ ($CDCl_3$) 166.2 (CO), 153.5, 151.8 (C-6, C-6'), 141.7 (C-7), 137.5 (C-1), 127.6, 127.2, 121.9 (C), 131.3, 129.6, 125.2, 122.3, 118.5, 114.9 (CH), 107.7 (C-α), 56.7 (OMe), 25.6 (NMe); *m/z* (%) 279 (M^+, 100), 264 (31), 236 (24); IR ν 1699, 1663 cm^{-1}; UV (EtOH) (log ε) 394 (3.64), 306 sh (4.07), 290 (4.27), 248 (4.24), 222 (4.21) nm; Anal. Calcd. for $C_{17}H_{13}NO_3$: C 73.11, H 4.69, N 5.01, found C 72.80, H 4.59, N 4.92.

4',5'-Demethoxy-1,α-dihydro-aristoyagonine 12c. Yellow-brown crystals, 0.14 g, 25%; mp 169-171 ºC (EtOH); ^{1}H-NMR δ ($CDCl_3$) 7.49 (1H, d, J=8.3, Ar-H), 7.32-6.95 (5H, m, Ar-H), 4.50 (1H, dd, J=11.3 and 2.7, H-1), 3.95 (3H, s, Me), 3.41 (1H, dd, J=13.6 and 2.7, H<u>C</u>H), 3.14 (3H, s, NMe), 2.87 (1H, brt, J=13.6, HC<u>H</u>); ^{13}C-NMR δ ($CDCl_3$) 167.9 (CO), 154.0, 151.7, 139.3, 132.8, 124.5, 123.1 (C), 132.5, 128.6, 123.3, 121.7, 118.1, 112.3 (CH), 59.7 (OMe), 56.6 (C-1), 38.0 (CH_2), 27.2 (NMe); *m/z* (%) 281 (M^+, 100), 250 (47), 175 (45); IR ν 1688 cm^{-1}; UV ($CHCl_3$) (log ε) 294 sh (3.47), 266 (4.33), 244 (4.34) nm; Anal. Calcd. for $C_{17}H_{15}NO_3$: C 73.57, H 5.38, N 4.98, found C 72.54, H 5.18, N 4.72.

Reaction of chloroxanthene 9b with Mg/THF.

Over a solution of 9b (0.040 g, 0.13 mmol) in THF (3 mL) was added Mg (4 mg, 0.16 mmol). After refluxing for 12 h, the solution was diluted with wet THF and filtered. The filtrates were washed with water, dried and concentrated in vacuo to obtain 10b. This compound decomposes in air to 11b.

2,3-Methylenedioxy-5-methoxy-9-methylenexanthene 10b. Syrup, 0.035 g, quantitative; ^{1}H-NMR δ ($CDCl_3$) 7.28 (1H, dd, J=8.0 and 1.2, Ar-H), 7.08 (1H, s, Ar-H), 7.02 (1H, t, J=8.0, H-7), 6.85 (1H, dd, J=8.0 and 1.2, Ar-H), 6.74 (1H, s, Ar-H), 5.96 (2H, s, OCH_2O), 5.34 (1H, s, HCH), 5.24 (1H, s, HCH), 3.92 (3H, s, OMe); ^{13}C-NMR δ ($CDCl_3$) 148.7, 148.2, 145.8, 144.5, 132.4, 121.5, 114.0 (C), 101.9 (OCH_2O), 98.6 (C=CH_2), 122.8, 115.4, 110.8, 101.9, 98.6 (CH), 56.1 (OMe); *m/z* (%) 268 (M^+, 100), 253 (32); IR ν 1632 cm^{-1}, UV ($CHCl_3$) (log ε) 346 (3.50), 304 (3.56), 250 (4.04) nm; HRMS calcd. for $C_{16}H_{12}O_4$ (M^+) *m/z* 268.0736, found 268.0735.

2,3-Methylenedioxy-5-methoxyxanthone 11b. Brown solid; mp 196-8 ºC; ^{1}H-NMR δ ($CDCl_3$) 7.89 (1H, m, Ar-H), 7.64 (1H, s, Ar-H), 7.33-7.18 (2H, m, Ar-H), 7.02 (1H, s, Ar-H), 6.11 (2H, s, OCH_2O), 4.02 (3H, s, OMe); ^{13}C-NMR δ ($CDCl_3$) 175.9 (CO), 153.7, 153.6, 148.4, 146.4, 145.4 (C), 122.2, 116.4 (C-8a, C-1a), 123.4, 117.5, 114.7, 103.0, 98.2 (CH), 102.4 (OCH_2O), 56.4 (OMe); *m/z* (%) 270 (M^+, 100), 255 (50); IR ν 1651 cm^{-1}; UV (log ε) 358 (3.35), 312 (3.20), 252 (3.90) nm; HRMS calcd. for $C_{15}H_{10}O_5$ (M^+) *m/z* 270.0528, found 270.0521.

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