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Total Synthesis of Cularine Alkaloids Via Dibenzoxepines as Key Intermediates#

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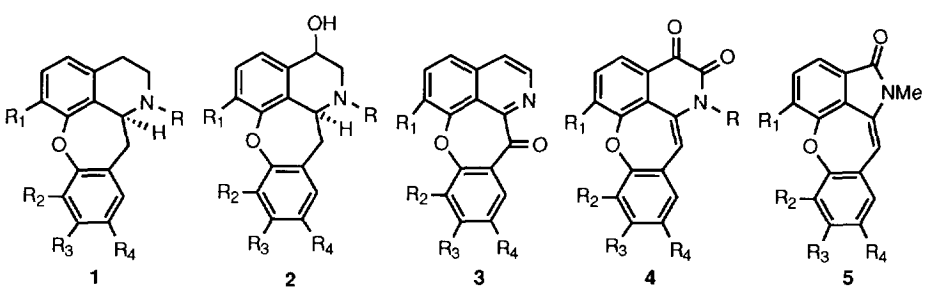
Abstract: The total synthesis of several cularine alkaloids (cularine, oxocularine, dioxocularine and 4-hydroxycularine) via 10,11-dihydrodibenz(b,f)oxepin-10-ones as key intermediates is reported.

The cularines are a group of isoquinoline alkaloids with a dibenzoxepine unit in their molecular skeleton.[1] Besides the largest subgroup, the simple cularines (**1**), this group includes other, highly oxidized members: the 4-hydroxycularines (**2**), the oxocularines (**3**), the dioxocularines (**4**) and the aristocularines (**5**). Since these compounds are present in only minute amounts in their natural plant sources, we set out to achieve their efficient synthesis.



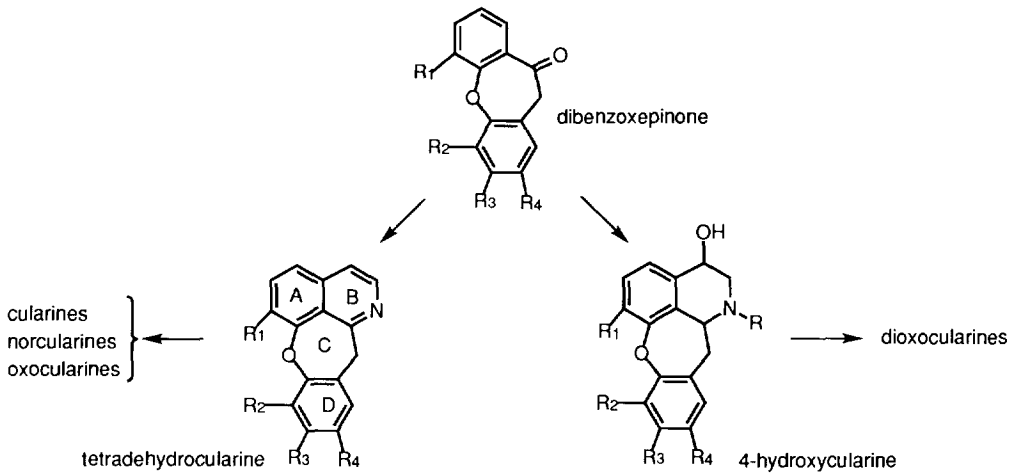
1 **2** **3** **4** **5**

Scheme 1

The main general approach to the synthesis of simple cularines involves the preparation of an appropriately substituted 1-benzylisoquinoline and subsequent formation of the oxepine system via intramolecular Ullmann condensation.[2] However, this method fails when applied to the preparation of tetradehydrocularines, which are versatile intermediates for the synthesis of various other types of cularines.[3] This led us to approach tetradehydrocularines by assembling ring B on a dibenzoxepinone precursor (Scheme

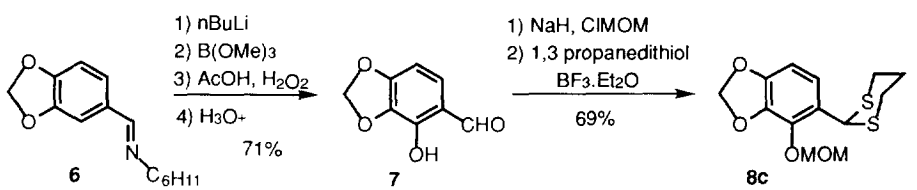
This paper is dedicated to Prof. U. K. Pandit on the occasion of his 65th birthday

2); dibenzoxepinones had already proved to be a useful basis for synthesis of aristocularines (5),[4] and turned out also to be useful for the preparation of 4-hydroxy and 3,4-dioxocularines.

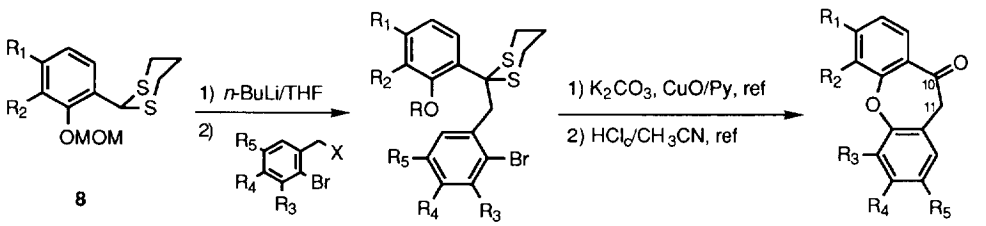


Scheme 2

In a preliminary communication[5] we reported the preparation of dibenzoxepinones **11a** and **11b** by a new procedure based on the formation of the C_{10}-C_{11} bond by alkylation of the lithium derivative of the dithiane **8** with the halide **9** to give the coupling product **10** (Scheme 4); deprotection of the phenol, Ullmann condensation and final hydrolysis led to dibenzoxepinones **11** in the yields indicated in Table 1. This approach is a significant improvement on classical methods[6a] since it gives better yields and allows the preparation of appropiately substituted dibenzoxepinones; previously, synthesis of dibenzoxepinones substituted with benzyloxy groups,[6b] as needed for phenolic cularines, suffered from low yields in the strongly acidic conditions of the cyclisation step. Thus, our procedure has also been satisfactorily used to synthesize the tetrasubstituted dibenzoxepinone **11c** from **8c** and **9c**. Dithiane **8c** was prepared as indicated in Scheme 3 from piperonal cyclohexylimine (**6**): **6** was metalated at position 2 with *n*-BuLi,[7] the aryl lithio derivative was quenched with $B(OMe)_3$, the resulting crude was treated with hydrogen peroxide, hydrolysis of the imine group led to compound **7** in 71% overall yield (a great improvement on the 25% yield of the four step sequence previously used to prepare this compound)[8] and protection of the phenol as a methoxymethyl ether followed by thioacetalization afforded **8c**. After formation of **10c** as in Scheme 4 and deprotection of the phenol, dibenzoxepinone **11c** was obtained in a 47% yield by Ullmann condensation and hydrolysis.



Scheme 3



8 9 10 11

Scheme 4

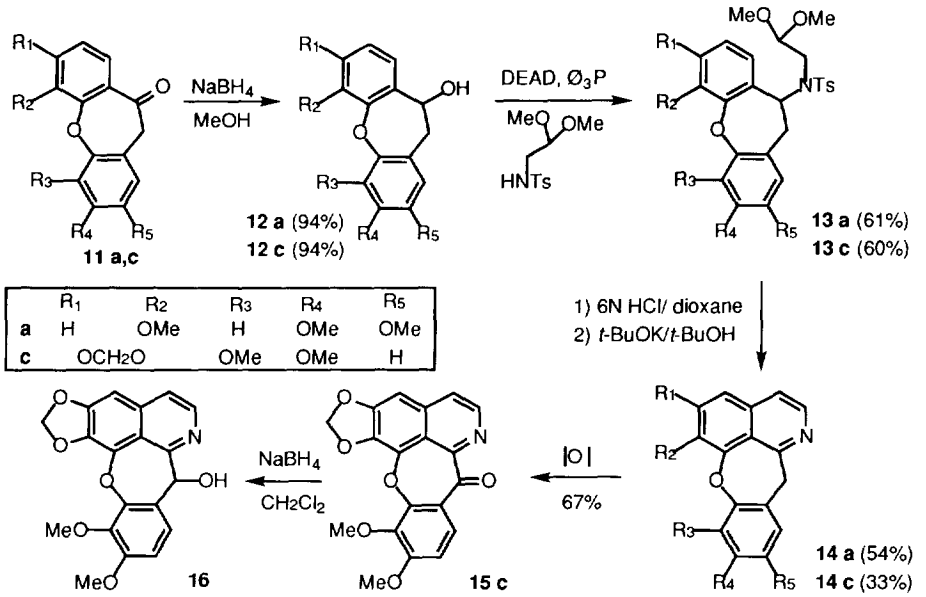
Table 1

	R_1	R_2	R_3	R_4	R_5	X	Yield of **10** (%)	Yield of **11** (%)
a	H	OMe	H	OMe	OMe	Br	57 (R=H)	65
b	H	OMe	OMe	OMe	H	Cl	64 (R=H)	63
c	OCH_2O		OMe	OMe	H	Cl	61 (R=MOM)	47

With **11a-c** in hand, we turned our attention to the construction of the isoquinoline heteroring on the dibenzoxepinone system.

The synthesis of tetradehydrocularine **14a** from dibenzoxepinone **11a** had previously been carried out in very low yield (8%), by a Pomerantz-Fritsch cyclisation.[6c] We found a better approach via the ketal **13a** (Scheme 5), which was prepared in 61% yield by Mitsunobu condensation[9] of the alcohol **12a** with $HN(Ts)CH_2CH(OMe)_2$; acid cyclisation of **13a** followed by basic treatment afforded **14a** in 54% yield. In an analogous sequence, **12c** led in 60% yield to the acetal **13c**, which was cyclized to the corresponding tetradehydrocularine derivative **14c** in 33% yield; the major product (45%) of this last reaction was the dibenzoxepine resulting from β-elimination of the sulphonamide, which is favoured by the presence of the oxygen of the methylenedioxy group located *para* to the benzylic position.

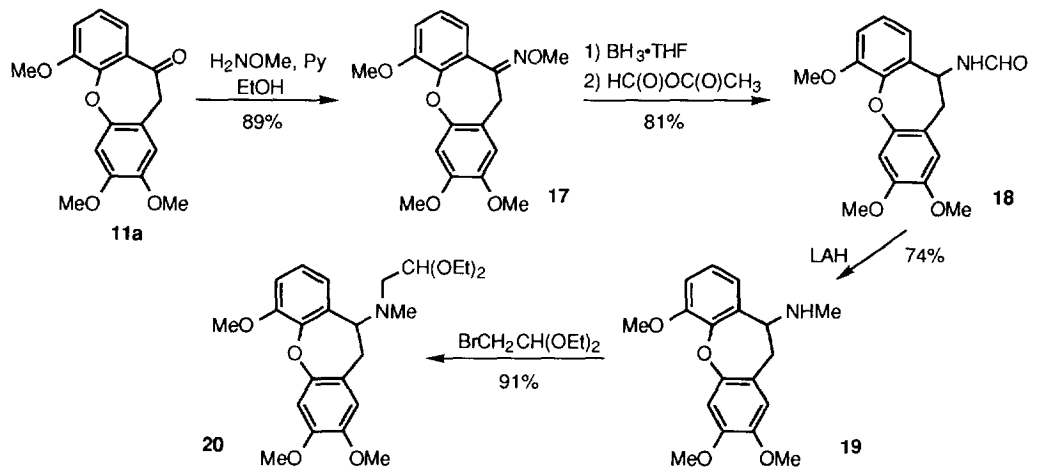
The tetradehydrocularine **14a** can easily be transformed[3] to cularine (**1**, R_1=R_3=R_4=OMe, R_2=H, R=Me) by methyl iodide treatment followed by sodium borohydride reduction; to oxocularine (**15a**) by Fremy's salt oxidation; and to N-norcularine (**1**, R_1=R_3=R_4=OMe, R=R_2=H) by catalytic hydrogenation. This illustrates the great value of tetradehydrocularines as synthetic intermediates. Compound **14c** was oxidized to the non-natural oxocularine derivative **15c** in 67% by refluxing in pyridine under O_2, and $NaBH_4$ reduction of the carbonyl group of **15c** in an aprotic medium afforded the α-hydroxytetradehydrocularine derivative **16**.[10] The structure of **16** has previously been attributed to the alkaloid linaresine,[11] but we found that the ^{1}H-NMR, MS, IR and UV spectra of **16** actually differ considerably from those of linaresine[12] whose structure should therefore be re-investigated. Indeed, our synthetic α-hydroxy compound **16** is easily oxidized by air to the oxocompound **15c**, which suggests that any α-hydroxytetradehydrocularines present in natural sources are unlikely to survive the isolation process.



	R1	R2	R3	R4	R5
a	H	OMe	H	OMe	OMe
c	OCH_2O		OMe	OMe	H

Scheme 5

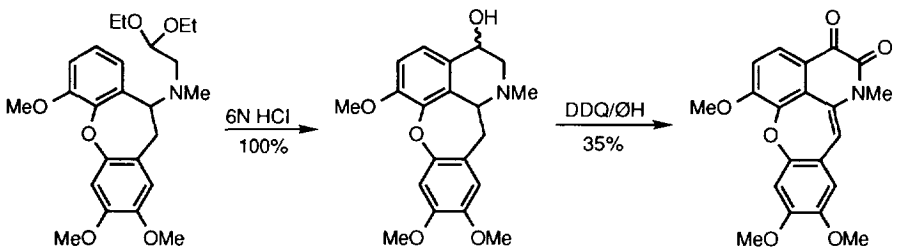
As mentioned above, dibenzoxepinones have also proved useful for synthesis of 4-hydroxy and 3,4-dioxocularines. For this, the nitrogen ring was constructed via the aminoacetal **20**, which was obtained from dibenzoxepinone **11a** in 48% overall yield as follows (Scheme 6): compound **11a** was refluxed in ethanol with O-methylhydroxylamine hydrochloride and pyridine, affording the O-methyl oxime **17**; borane reduction of **17**, followed by N-formylation of the resulting primary amine, yielded formamide **18**; and the N-methyl amine **19** obtained by LAH reduction of **18** was then alkylated with bromo acetaldehyde diethyl acetal to yield compound **20**.



Scheme 6

Acid cyclisation (6N HCl) of acetal **20** afforded, in almost quantitative yield, a 1:1 epimeric mixture of O-methyllimousamine[13] (**21**). In a previous total synthesis of 4-hydroxisarcocapnine,[2] the hydroxilation step led to a 76% yield of a 1:9 mixture of epimers at C_4, the natural configuration being disfavoured; also, a partial synthesis[14] of O-methyllimousamine (**21**) from cularidine (**1**, R_1=OH, R_2=H, R_3=R_4=OMe, R=Me) has been published, in which the hydroxilation step leds to a 33% yield of a 2:3 mixture of epimers at C_4, again the natural configuration being disfavoured.

Finally, oxidation of the epimeric mixture of **21** by DDQ in refluxing benzene[14] yielded dioxocularine (**22**).[15]



20 **21** **22**

Scheme 7

To sum up, dibenzoxepinones are versatile intermediates for the total synthesis of several cularine alkaloids including cularines, N-norcularines, oxocularines, 4-hydroxycularines, 3,4-dioxocularines and aristocularines.

EXPERIMENTAL

^1H and ^{13}C nmr spectra were recorded at 250.13 and 62.83 MHz respectively on a Bruker WM-250 spectrometer; the solvent for nmr spectra was $CDCl_3$ unless otherwise stated, and chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane. Mass spectra were recorded at an ionization voltage of 70 eV. Melting points are uncorrected.

2-(3-Methoxy-2-methoxymethoxyphenyl)-1,3-dithiane (8a, 8b). 3-Methoxy-2-methoxymethoxy benzaldehyde[16] (36.5 g, 0.186 mol) and Na_2SO_4 (15 g) were stirred with 150 ml of anhydrous chloroform. BF_3•Et_2O (4.5 ml, 0.037 mol) and 1,3-propanedithiol (19.6 ml, 0.195 mol) were sequentially added to the cooled mixture (0°C) and stirring was continued for 24h at room temperature. Na_2SO_4 was filtered off and the organic phase was washed with 10% NaOH (2x25 ml) and water (20 ml), and dried (Na_2SO_4). The residue obtained after removing the solvent was crystallized from ether/hexane as 35 g (65%) of **8a**, mp 71-74°C. IR (KBr): 3000-2800, 1590, 1480, 1440, 1310, 1280. ^1H NMR (ppm): 7.21 (dd, J= 7.9 and J=1.4, 1H, Ar-H), 7.07 (t, J= 8.0, 1H, Ar-H), 6.84 (dd, J= 8.0 and J=1.4, 1H, Ar-H), 5.71 (s, 1H, CH), 5.17 (s, 2H, $\underline{CH_2}$OMe), 3.81 (s, 3H, ArOMe), 3.63 (s, 3H, OMe),3.07-2.91 (m, 4H, 2xSCH_2), 2.12-

1.94 (m, 2H, CH_2). ^{13}C NMR (ppm): 152.0 (C), 142.2 (C), 133.3 (C), 124.7 (CH), 121.0 (CH), 112.4 (CH), 99.1 ($\underline{C}H_2OMe$), 57.6 (ArCH), 55.8 (ArOMe), 44.5 (CH_3), 32.3 (2xSCH_2), 25.1 (CH_2). MS: m/e(%) 286 (M^+, 14), 241 (100), 180 (23), 167 (96), 136 (21). Anal. Calcd for $C_{13}H_{18}O_3S_2$, C 54.51, H 6.33; found: C, 54.64, H 6.62.

2-(2-Methoxymethoxy-3,4-methylenedioxyphenyl)-1,3-dithiane (8c)

2-Hydroxy-3,4-methylenedioxy benzaldehyde (7). Under Ar 51 g (0.21 mol) of piperonal cyclohexylimine (**6**)[7] were placed in 0.75 ml of anhydrous THF in a flame-dried flask, and the mixture was cooled to -75°C. To this solution was added 2.5M *n*-BuLi (95 ml, 0.24 mol) and stirring was continued for 15 min; $B(OMe)_3$ (28 ml, 0.24 mol) was added and the resulting mixture was warmed to 0°C for 1h; then glacial AcOH (20 ml) was added, followed by H_2O_2 (30% vol., 50 ml) and the solution allowed to warm to room temperature over 12h. The THF was evaporated, and the residue was treated with methylene chloride (100 ml), washed with brine (20 ml), 5% aqueous $Na_2S_2O_5$ (3x20 ml) and brine (20 ml), and dried (Na_2SO_4). After evaporation of the solvent, the residue was dissolved in 300 ml of THF and refluxed with 60 ml of 6N HCl for 6h. The mixture was cooled, THF evaporated and the residue taken up in methylene chloride; the organic phase was extracted with 10% NaOH (4x25 ml), and the combined aqueous extracts were acidified with 20% HCl and extracted with methylene chloride (3x50 ml). This organic phase was washed with water (30 ml) and dried (Na_2SO_4), and the solvent was evaporated to dryness, affording 26 g (71%) of **7** as a yellow solid, mp 115-116°C (lit. 115-116°C).[8] ^1H NMR (ppm): 10.99 (s, 1H, OH), 9.73 (s, 1H, CHO); 7.16 (d, J= 8.2, 1H, Ar-H), 6.58 (d, J= 8.2, 1H, Ar-H), 6.10 (s, 2H, OCH_2O).

2-Methoxymethoxy-3,4-methylenedioxy benzaldehyde. 80% NaH (6.9 g, 0.23 mol) was placed under Ar in a flame-dried flask and washed twice with anhydrous THF (2x5 ml). More THF (400 ml) was added and the mixture was cooled to 0°C. A solution of **7** (25.5 g, 0.15 mol) in 250 ml of THF was slowly added and the resulting mixture was vigorously stirred at room temperature for 3h. Then chloromethylmethyl ether (13 ml, 0.17 mol) was added and the solution was stirred overnight. 50 ml of 10% NaOH were added and the THF was evaporated. The residue was extracted in methylene chloride (100 ml), washed with 10% NaOH and water (25 ml), and dried (Na_2SO_4). After evaporation of the solvent, 31.9 g of 2-methoxymethoxy-3,4-methylenedioxy benzaldehyde were obtained, mp 47.5°C (ether/hexane). IR (KBr): 3000-2800, 1670 (CO), 1465, 1280, 1155. ^1H NMR (ppm): 10.28 (s, 1H, CHO), 7.49 (d, J= 8.2, 1H, Ar-H), 6.66 (d, J= 8.2, 1H, Ar-H), 6.06 (s, 2H, OCH_2O), 5.39 (s, 2H, CH_2OMe), 3.54 (s, 3H, OMe). ^{13}C NMR (ppm): 187.7 (CO), 154.3 (C), 142.2 (C), 136.7 (C), 124.4 (CH), 123.5 (C), 103.9 (CH), 102.0 (OCH_2O), 96.9 ($\underline{C}H_2OMe$), 57.0 (CH_3). MS: m/e(%) 210 (M^+, 7), 164 (19), 95 (20), 81 (26), 43 (100). HRMS Calcd for $C_{10}H_{10}O_5$, 210.0529; found, 210.0528.

2-(2-Methoxymethoxy-3,4-methylenedioxyphenyl)-1,3-dithiane (8c). 2-Methoxymethoxy-3,4-methylenedioxy benzaldehyde (27.5 g, 0.131 mol) and Na_2SO_4 (15 g) were stirred with 125 ml of anhydrous chloroform. $BF_3{\bullet}Et_2O$ (1.28 ml, 0.010 mol) and 1,3-propanedithiol (13.8 ml, 0.137 mol) were sequentially added to the cooled mixture (0°C) and stirring was continued for 24h at room temperature. Na_2SO_4 was filtered off and the organic phase was washed with 10% NaOH (2x25 ml) and water (20 ml) and dried (Na_2SO_4). The

residue obtained after removing the solvent was crystallized from CH_2Cl_2/hexane as 27.8 g (71%) of **8c**, mp 98-99°C. IR (KBr): 3000-2800, 1475, 1275, 1150. ^1H NMR (ppm): 7.12 (d, J= 8.2, 1H, Ar-H), 6.59 (d, J= 8.2, 1H, Ar-H), 5.94 (s, 2H, OCH_2O), 5.59 (s, 1H, Ar-CH), 5.34 (s, 2H, CH_2OMe), 3.57 (s, 3H, OMe), 3.14-2.84 (m, 4H, 2xSCH_2), 2.25-1.80 (m, 2H, CH_2). ^{13}C NMR (ppm): 148.8 (C), 136.7 (C), 136.4 (C), 125.3 (C), 122.4 (CH), 103.9 (CH), 101.1 (OCH_2O), 96.9 ($\underline{C}H_2OMe$), 57.1 (OMe), 43.5 (CH), 32.4 (2xSCH_2), 25.0 (CH_2). MS: m/e(%) 300 (M^+, 2), 255 (16), 181 (42), 43 (100). Anal. Calcd for $C_{13}H_{16}O_4S_2$, C 51.84, H 5.25; found, C 51.98, H 5.37.

2-(2-Bromo-4,5-dimethoxybenzyl)-2-(2-hydroxy-3-methoxyphenyl)-1,3-dithiane (10a). Following the procedure described below for **10b**, reaction of **8a** and **9a**[17] afforded **10a** in 57% yield as a white solid, mp 144-146°C (EtOAc/hexane). IR (KBr): 3500-3400, 3000, 2960, 2935, 2900, 2830, 1600, 1580, 1495. ^1H NMR (ppm): 8.81 (s, 1H, OH), 7.26 (dd, J= 8.1 and J=1.6, 1H, Ar-H), 6.94 (s, 1H, Ar-H), 6.91 (dd, J= 8.1 and J=1.5, 1H, Ar-H), 6.80 (t, J=8.1, 1H, Ar-H), 6.00 (s, 1H, Ar-H), 3.90 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.56 (s, 2H, Ar-CH_2), 3.47, (s, 3H, OMe), 2.92-2.67 (m, 4H, 2xS-CH_2), 1.97 (m, 2H, CH_2). ^{13}C NMR (ppm): 149.4 (C), 148.5 (C), 147.2 (C), 146.1 (C), 125.9 (C), 124.7 (CH), 123.4 (C), 119.0 (CH), 116.1 (C), 115.0 (CH), 114.9 (CH), 111.9(CH), 59.6 (CS_2), 56.2 (OMe), 55.8 (OMe), 55.3 (OMe), 45.3 ($ArCH_2$), 27.9 (2xSCH_2), 24.0 (CH_2). MS: m/e(%) 391 (3), 317 (5), 243(17), 241 (100), 167 (13), 152 (8). Anal. Calcd for $C_{20}H_{23}BrO_4S_2$, C 50.95, H 4.92; found C 51.00, H 4.96.

2-(2-Bromo-4,5-dimethoxybenzyl)-2-(3-hydroxy-2-methoxyphenyl)-1,3-dithiane (10b). A cooled solution (-80°C) of **8b** (12 g, 41.9 mmol) in 180 ml of anhydrous THF was treated with 1.5 M *n*-BuLi (28 ml, 42 mmol). Stirring was continued for 2h, and then a solution of 11.1 g (41.9 mmol) of **9b**[18] in 50 ml of anhydrous THF was cannulated into the reaction flask. The resulting mixture was allowed to warm to room temperature for 4h and then NH_4Cl aq was added. THF was evaporated, the residue was extracted with methylene chloride (70 ml) and the organic phase washed with water (2x25 ml), dried (Na_2SO_4) and concentrated. The crude was dissolved in a mixture of 5% HCl and THF (1:5) and stirred at room temperature for 20h. Methylene chloride (100 ml) was added and the reaction mixture was washed with water (2x25 ml), dried (Na_2SO_4) and concentrated. The solid residue was chromatographed (SiO_2; 1:1, CH_2Cl_2/hexane) affording 12.5 g (64%) of **10b** as a white solid, mp 89-93°C (CH_2Cl_2/hexane). IR (KBr): 3170, 2940, 2840, 1600, 1580, 1490, 1460, 1280, 1250, 1230, 1040. ^1H NMR (ppm): 8.87 (s, 1H, OH), 7.29 (dd, J= 8.5 and J=1.4, 1H, Ar-H), 6.90 (dd, J= 8.0 and J=1.4, 1H, Ar-H), 6.78 (t, J=8.0, 1H, Ar-H), 6.66 (s, 2H, 2xAr-H), 3.89 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.77, (s, 3H, OMe), 3.58 (s, 2H, Ar-CH_2), 2.72 (m, 4H, 2xS-CH_2), 1.93 (m, 2H, CH_2). ^{13}C NMR (ppm): 152.7 (C), 149.2 (C), 146.3 (C), 146.1 (C), 127.7 (CH), 126.9 (C), 124.3 (CH), 123.1 (C), 122.5 (C), 118.9 (CH), 111.8 (CH), 110.1(CH), 60.1 (OMe), 59.7 (CS_2), 56.1 (OMe), 55.8 (OMe), 45.8 ($ArCH_2$), 27.9 (2xSCH_2), 24.0 (CH_2). MS: m/e(%) 472 (1), 470 (M^+, 1), 391 (2), 317 (21), 241 (100). Anal. Calcd for $C_{20}H_{23}BrO_4S_2$, C 50.95, H 4.92, S 13.60; found, C 51.10, H 5.02, S 13.80.

2-(2-Bromo-3,4-dimethoxybenzyl)-2-(2-methoxymethoxy-3,4-methylenedioxyphenyl)-1,3-dithiane(10c). A cooled solution (-40°C) of **8c** (25.3 g, 84.2 mmol) in 400 ml of anhydrous THF was treated with 1.47 M *n*-BuLi (58 ml, 85.3 mmol). Stirring was continued for 2h and then a solution of 22.3 g

(84.2 mmol) of **9c**[18] in 80 ml of anhydrous THF was cannulated into the reaction flask. The resulting mixture was allowed to warm to room temperature for 4h and 5% HCl (10 ml) was added. THF was evaporated, the residue was extracted with methylene chloride (100 ml), and the organic phase was washed with water (2x25 ml), dried (Na_2SO_4) and concentrated. The solid residue was chromatographed (SiO_2; 3:7, EtOAc/hexane) affording 27.1 g (61%) of **10c** as a white solid, mp 141-143°C (EtOAc/hexane). IR (KBr): 3000-2800, 1590, 1490, 1470, 1400, 1275, 1175, 1055, 1030. ^{1}H NMR (ppm): 7.29 (d, J= 8.5, 1H, Ar-H), 6.60 (d, J= 8.6, 1H, Ar-H), 6.50 (m, 2H, 2xAr-H), 6.00 (s, 2H, OCH_2O), 5.36 (s, 2H, CH_2OMe), 3.95 (s, 2H, Ar-CH_2), 3.80 (s, 3H, ArOMe), 3.79 (s, 3H, ArOMe), 3.63, (s, 3H, OMe), 2.75 (m, 4H, 2xSCH_2), 1.94 (m, 2H, CH_2). ^{13}C NMR (ppm): 152.2 (C), 149.1 (C), 146.1 (C), 138.8 (C), 138.5 (C), 129.0 (C), 126.7 (CH), 126.6 (C), 125.8 (CH), 122.6 (C), 110.2 (CH), 101.8 (CH), 101.4 (OCH_2O), 97.3 ($\underline{C}H_2OMe$), 60.2 (OMe), 58.3 (CS_2), 57.9 (OMe), 55.8 (OMe), 44.8 ($ArCH_2$), 27.8 (2xSCH_2), 24.4 (CH_2). MS: m/e(%) 530 (1), 528 (M^+, 1), 449 (M^+-Br, 1), 300 (22), 299 (100). Anal. Calcd for $C_{22}H_{25}BrO_6S_2$, C 49.90, H 4.76; found, C 50.01, H 4.69.

10,11-Dihydro-2,3,6-trimethoxy-dibenz(b,f)oxepin-10-one (11a). By the same procedure as for the synthesis of **11b**, **11a** was obtained in 65% yield as a light yellow solid, mp 132-134°C (MeOH) (lit 133-134°C).[6a] ^{1}H NMR (ppm): 7.61 (dd, J= 7.3 and J=2.4, 1H, Ar-H), 7.13-7.09 (m, 2H, 2xAr-H), 6.90 (s, 1H, Ar-H), 6.75 (s, 1H, Ar-H), 4.00 (s, 2H, $ArCH_2$), 3.99 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.86 (s, 3H, OMe)

10,11-Dihydro-3,4,6-trimethoxy-dibenz(b,f)oxepin-10-one (11b). The dithiane **10b** (7 g, 14.8 mmol) was refluxed for 1h under Ar in anhydrous pyridine (40 ml) with CuO (3.54 g, 44.5 mmol) and K_2CO_3 (10.2 g, 74.2 mmol). After cooling, the mixture was filtered through celite and the solvent evaporated. CH_2Cl_2 (100 ml) was added, and the solution was washed with 10% HCl (3x20 ml) and water (20 ml), and dried (Na_2SO_4). After evaporation of the solvent, the residue was dissolved in acetonitrile (80 ml) and refluxed with conc. HCl (25 ml) and glyoxylic acid monohydrate (1.5 g, 27 mmol) for 2h. To the cooled mixture were added methylene chloride (50 ml) and brine (20 ml), and the phases were separated. The organic phase was further washed with brine (20 ml), 5% K_2CO_3 (20 ml) and brine (20 ml), and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was chromatographed (SiO_2, CH_2Cl_2) to afford 2 g (63%) of **11b** as a light yellow solid, mp 98-99°C (ether/hexane). IR (KBr): 3090, 3000, 2940, 2840, 1680, 1600, 1580, 1500, 1470. ^{1}H NMR (ppm): 7.62 (dd, J= 7.5 and J=2.1, 1H, Ar-H), 7.19-7.08 (m, 2H, 2xAr-H), 6.95 (d, J= 8.4, 1H, Ar-H), 6.74 (d, J= 8.4, 1H, Ar-H), 4.03 (s, 2H, $ArCH_2$), 4.02 (s, 3H, OMe), 3.96 (s, 3H, OMe), 3.84 (s, 3H, OMe). ^{13}C NMR (ppm): 190.6 (C), 153.0 (C), 151.6 (C), 151.1 (C), 150.2 (C), 141.3 (C), 127.7 (C), 123.5 (CH), 123.1 (CH), 121.5 (CH), 120.3 (C), 117.2 (CH), 109.9 (CH), 61.6 (OMe), 56.6 (OMe), 56.3 (OMe), 47.6 (CH_2). Ms: m/e(%) 300 (M^+, 78), 285 (24), 269 (100), 254 (9), 241 (10), 229 (6). Anal. Calcd for $C_{17}H_{16}O_5$, C 67.99, H 5.37; found, C 68.13, H 5.50.

10,11-Dihydro-3,4-dimethoxy-6,7-methylenedioxy-dibenz(b,f)oxepin-10-one (11c). The dithiane **10c** (18 g, 34.0 mmol) was dissolved in 50 ml of THF and 25 ml of MeOH, and the solution was refluxed with 10% HCl (25 ml) for 1h. After cooling and evaporation of the solvent methylene chloride was added (75 ml) and the organic phase was washed with water (25 ml) and dried (Na_2SO_4). The residue obtained after evaporation was refluxed for 1h under Ar in anhydrous pyridine (200 ml) with CuO (9 g, 113.2 mmol)

and K_2CO_3 (26 g, 188.1 mmol). After cooling, the mixture was filtered through celite and the solvent evaporated. CH_2Cl_2 (100 ml) was added, and the solution was washed with 10% HCl (3x20 ml) and water (20 ml), and dried (Na_2SO_4). After evaporation of the solvent, the residue was dissolved in acetonitrile (100 ml) and refluxed with conc. HCl (50 ml) and glyoxylic acid monohydrate (6.7 g, 72.8 mmol) for 2h. To the cooled mixture were added methylene chloride (50 ml) and brine (20 ml), and the phases were separated. The organic phase was further washed with brine (20 ml), 5% K_2CO_3 (20 ml) and brine (20 ml), and dried (Na_2SO_4). Evaporation of the solvent gave a solid residue which was chromatographed (SiO_2, CH_2Cl_2) to afford 5.02 g (47%) of **11c** as a light yellow solid, mp 181-183°C (MeOH). IR (KBr): 3000-2850, 1675 (CO), 1615, 1500, 1455. ^1H NMR (ppm): 7.68 (d, J= 8.6, 1H, Ar-H), 6.95 (d, J= 8.4, 1H, Ar'-H), 6.74 (d, J= 8.4, 1H, Ar'-H), 6.70 (d, J= 8.6, 1H, Ar-H), 6.17 (s, 2H, OCH_2O), 4.00 (s, 2H, Ar'CH_2), 3.99 (s, 3H, OMe), 3.85 (s, 3H, OMe). ^{13}C NMR (ppm): 189.5 (CO), 153.5 (C), 152.9 (C), 150.2 (C), 144.1 (C), 141.2 (C), 138.2 (C), 125.7 (CH), 123.3 (CH), 122.7 (C), 120.1 (C), 109.9 (CH), 104.9 (CH), 102.8 (OCH_2O), 61.8 (CH_2), 56.3 (OMe), 47.4 (OMe). MS: m/e(%) 314 (M^+, 50), 283 (100), 241 (10), 200 (10), 95 (20). Anal. Calcd for $C_{17}H_{14}O_6$, C 64.96, H 4.49; found, C 64.81, H 4.48.

10,11-Dihydro-10-hydroxy-2,3,6-trimethoxy-dibenz(b,f)oxepine (12a). To a solution of the dibenzoxepinone **11a** (0.5 g, 1.7 mmol) in 20 ml of methanol, sodium borohydride was added in small portions with stirring at 4°C until analysis on silica gel showed no remaining ketone. The solvent was evaporated, water (10 ml) was added and the product was extracted with methylene chloride (2x15 ml). The organic layer was washed with water (10 ml) and dried (Na_2SO_4), and the solvent evaporated to give 0.47 g (94%) of **12a** as a white solid, mp 179-181°C (lit 169-170°C).[19] ^1H NMR (ppm): 7.11-7.00 (m, 2H, 2xAr-H), 6.88-6.84 (m, 2H, 2xAr-H), 6.66 (s, 1H, Ar-H), 5.20 (dt, J= 8.0 and 3.3, 1H, Ar-CH), 3.92 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.44 (dd, J= 14.7 and 3.3, 1H, Ar-CH), 3.10 (dd, J= 14.7 and 7.8, 1H, Ar-CH), 2.18 (d, J=8.4, 1H, OH).

10,11-Dihydro-10-hydroxy-3,4-dimethoxy-6,7-methylenedioxy-dibenz(b,f)oxepine (12c). A solution of **11c** (1 g, 3.2 mmol) in 40 ml of methanol was treated with sodium borohydride as above, affording 0.94 g (94%) of **12c** as an oil. IR (film): 3500-3100, 3000-2800, 1485, 1450, 1260. ^1H NMR (ppm): 6.92 (s, 1H, Ar-H), 6.89 (s,1H, Ar-H), 6.68 (d, J= 8.3, 1H, Ar-H), 6.60 (d, J= 8.3, 1H, Ar-H), 6.04-6.03 (m, 2H, OCH_2O), 4.93 (dd, J= 7.1 and 2.6, 1H, Ar-C<u>H</u>-OH), 3.96 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.43 (dd, J= 13.8 and 2.6, 1H, Ar'-CH), 3.08 (dd, J= 13.8 and 7.1, 1H, Ar'-CH). ^{13}C NMR (ppm): 152.7 (C), 151.0 (C), 148.3 (C), 141.2 (C), 139.9 (C), 138.0 (C), 127.5 (C), 124.7 (CH), 124.1 (CH), 122.5 (C), 108.7 (CH), 104.6 (CH), 101.8 (OCH_2O), 69.0 (Ar-CH), 61.6 (OMe), 56.2 (OMe), 37.9 (Ar'-CH_2). MS: m/e (%) 316 (M^+, 13), 299 (7), 151 (39), 115 (30), 77 (73), 51 (100). HRMS Calcd for $C_{17}H_{16}O_6$, 316.0946; found, 316.0946.

10-(N-tosyl aminoacetaldehyde dimethyl acetal)-10,11-dihydro-2,3,6-trimethoxy-dibenz(b,f)oxepine (13a). N-tosyl aminoacetaldehyde dimethyl acetal (0.43 g, 1.65 mmol) and triphenylphosphine (0.52 g, 1.98 mmol) were dissolved in 10 ml of dry THF. To this solution were sequentially added 0.2 g (0.66 mmol) of **12a** and 0.26 ml (1.66 mmol) of DEAD, and the resulting mixture was stirred under Ar for 3h. The solvent was evaporated and the residue was taken in CH_2Cl_2 and washed with

15% NaOH (5x15 ml) and water (1x15 ml). The crude so obtained was chromatographed (SiO_2; 2:3, EtOAc/hexane) to afford 0.21 g (61%) of **13a** as a white solid, mp: 164-166°C (ether). ^1H NMR (ppm): 7.83 (d, J= 8, 2H, 2xAr-H), 7.37 (d, J= 8, 2H, 2xAr-H), 6.82-6.75 (m, 3H, 3xAr-H), 6.53 (s, 1H, Ar-H), 6.44 (d, J= 7.4, 1H, Ar-H), 5.12 (dd, J= 11.9 and 4.5, 1H, Ar-CH-N), 4.40 (t, J= 5.0, 1H, C<u>H</u>$(OMe)_2$), 3.90 (s, 3H, ArOMe), 3.85 (s, 3H, ArOMe), 3.83 (s, 3H, ArOMe), 3.90-3.83 (m, 1H, Ar-CH), 3.35-3.15 (2H, N-CH_2), 3.28 (s, 3H, OMe), 3.18 (s, 3H, OMe), 2.59 (dd, J= 13.2 and 4.5, 1H, Ar-CH), 2.47 (s, 3H, Ar-CH_3). ^{13}C NMR (ppm): 153.1 (C), 151.7 (C), 148.2 (C), 147.6 (C), 146.3 (C), 143.6 (C), 137.8 (C), 129.7 (2xCH-Ar), 128.9 (C), 127.5 (2xCH-Ar), 123.5 (CH), 123.0 (CH), 121.8 (C), 112.2 (CH), 111.1 (CH), 105.2 (CH), 103.7 ($CH(OMe)_2$), 57.8 (CH-N), 56.3 (OMe), 56.2 (OMe), 56.1 (OMe), 54.5 (OMe), 54.0 (OMe), 47.2 (N-CH_2), 34.4 (Ar-CH_2), 21.4 (Ar-CH_3). IR (KBr) : 3100-2900, 1620, 1600, 1580, 1515, 1210, 1160. MS: m/e (%) 543 (M^+, 2), 388 (2), 285 (77), 271 (44), 91 (58), 75 (100). Anal. Calcd for $C_{28}H_{33}NO_8S$, C 61.86, H 6.11, N 2.57; found, C 61.74, H 6.32, N 2.51.

10-(N-tosyl aminoacetaldehyde dimethyl acetal)-10,11-dihydro-3,4-dimethoxy-6,7-methylenedioxy-dibenz(b,f)oxepine (13c). N-tosyl aminoacetaldehyde dimethyl acetal (0.41 g, 1.58 mmol) and triphenylphosphine (0.5 g, 1.91 mmol) were dissolved in 10 ml of dry THF. To this solution were sequentally added 0.2 g (0.63 mmol) of **12c** and 0.24 ml (1.53 mmol) of DEAD, and the resulting mixture was stirred under Ar for 3h. The residue was treated as above, affording 0.21 g (60%) of **13c** as a white solid, mp: 146-148°C (ether). ^1H NMR (ppm): 7.81 (d, J= 8.2, 2H, 2xAr-H), 7.38 (d, J= 8.2, 2H, 2xAr-H), 6.67 (d, J= 8.4, 1H, Ar-H), 6.66 (d, J= 8.4, 1H, Ar-H), 6.49 (d, J= 8.4, 1H, Ar-H), 6.47 (d, J= 8.4, 1H, Ar-H), 6.06-6.01 (m, 2H, OCH_2O), 5.04 (dd, J= 12.0 and 4.3, 1H, Ar-CH-N), 4.42 (t, J= 5.0, 1H, C<u>H</u>$(OMe)_2$), 3.93 (s, 3H, ArOMe), 3.82 (s, 3H, ArOMe), 3.72 (t, J= 12.0, 1H, ArCH), 3.29 (s, 3H, OCH_3), 3.20 (s, 3H, OCH_3), 2.48 (s, 3H, Ar-CH_3), 3.29-3.20 (m, 2H, N-CH_2), 2.53 (dd, J= 12.0 and 4.3, 1H, Ar-CH). ^{13}C NMR (ppm): 152.6 (C), 151.8 (C), 148.2 (C), 143.6 (C), 141.7 (C), 141.1 (C), 138.6 (C), 137.8 (C), 129.8 (2xCH), 127.4 (2xCH), 124.5 (CH), 124.2 (C), 123.1 (CH), 122.4 (C), 109.0 (CH), 104.6 (CH), 103.7 ($CH(OMe)_2$), 101.8 (OCH_2O), 61.6 (N-CH), 57.9 (OMe), 56.2 (OMe), 54.5 (O-Me), 54.0 (OMe), 47.0 (N-CH_2), 34.3 (ArCH_2), 21.4 (Ar-CH_3). IR (film): 3000-2900, 1470 , 1280, 1100. Ms: m/e (%) 557 (M^+, 22), 494 (28), 402 (100). Anal. Calcd for $C_{28}H_{31}NO_9S$, C 60.36, H 5.60, N 2.51; found, C 60.66, H 5.35, N 2.43.

Cyclisation of 13a. Synthesis of 6,9,10-trimethoxy-12H-[1]-benzoxepino[2,3,4-ij]isoquinoline (14a). A solution of 150 mg (0.27 mmol) of **13a** in 6 ml of dioxane was treated with 6N HCl (1.2 ml) and the resulting mixture was refluxed under Ar for 3h and then cooled and concentrated under reduced pressure. The residue was dissolved in 9 ml of anhydrous *tert*-butanol and refluxed with 0.6 g (5.3 mmol) of potassium *tert*-butoxide under Ar for 30h. The reaction mixture was poured onto water and extracted with methylene chloride (2x15 ml); the organic phase was washed with water (1x10 ml), dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed (SiO_2; 6:1, EtOAc/hexane) to afford 55 mg (54%) of **14a** as a solid, mp: 130-132°C (lit 131-133°C).[3] ^1H NMR (ppm): 8.16 (d, J= 5.8, 1H, Ar-H), 7.50 (s, 2H, 2xAr-H), 7.40 (d, J= 5.8, 1H, Ar-H), 6.94 (s, 1H, Ar-H), 6.90 (s, 1H, Ar-H), 4.60 (s, 2H, Ar-CH_2), 4.09 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.85 (s, 3H, OMe).

Cyclisation of 13c. Synthesis of 8,9-Dimethoxy-6,7-methylenedioxy-12H-[1]benzoxepino[2,3,4-ij]isoquinoline (14c). A solution of 300 mg (0.54 mmol) of **13c** in 6 ml of dioxane was treated with 6N HCl (1.2 ml) as before. The residue was dissolved in 9 ml of anhydrous *tert*-butanol and refluxed with 600 mg (5.34 mmol) of potassium *tert*-butoxide under Ar for 3h. Work up as above, followed by column chromatrography, led to a faster moving oily compound which was identified as 3,4-dimethoxy-6,7-methylenedioxy-dibenz(b,f)oxepine (70 mg, 45%). IR (film): 3050-2800, 1600, 1495, 1465, 1280. ^{1}H NMR (ppm): 6.81 (d, J=8.6, 1H, CH=C), 6.67 (d, J=8.6, 1H, CH=C), 6.59 (s, 2H, 2xAr-H), 6.48 (s, 2H, 2xAr-H), 6.04 (s, 2H, OCH_2O), 4.01 (s, 3H, OMe), 3.86 (s, 3H, OMe). ^{13}C NMR (ppm): 154.5 (C), 150.5 (C), 149.9 (C), 141.5 (C), 140.3 (C), 138.9 (C), 127.8 (CH), 127.5 (CH), 126.6 (C), 124.9 (C), 123.4 (CH), 122.0 (CH), 108.5 (CH), 104.9 (CH), 101.9 (OCH_2O), 61.5 (OMe), 56.1 (OMe). Ms: m/e (%) 298 (100), 283 (15), 240 (17), 212 (15), 197 (15). HRMS Calcd for $C_{17}H_{14}O_5$, 298.0841; found, 298.0841.

The tetradehydrocularine derivative **14c** was obtained as an amorphous white solid (60 mg, 33%). IR (film): 3000-2800, 1580 , 1500 , 1460, 1275, 1100. ^{1}H NMR (ppm): 8.14 (d, J= 5.7, 1H, Ar-H), 7.30 (d, J= 5.7, 1H, Ar-H), 7.06 (d, J= 8.4, 1H, Ar-H), 6.85 (s, 1H, Ar-H), 6.69 (d, J= 8.4, 1H, Ar-H), 6.19 (s, 2H, OCH_2O), 4.56 (s, 2H, Ar-CH_2), 4.02 (s, 3H, OMe), 3.83 (s, 3H, OMe). ^{13}C NMR (ppm): 154.7 (C), 152.7 (C), 151.4 (C), 150.1 (C), 141.5 (C), 140.9 (CH), 137.9 (C), 135.7 (C), 135.6 (C), 126.5 (C), 122.6 (CH), 119.4 (CH), 119.2 (C), 109.1 (CH), 102.3 (OCH_2O), 99.3 (CH), 61.6 (OMe), 56.2 (OMe), 42.1 (CH_2). MS: m/e (%) 337 (M^+, 100), 322 (59), 279 (30), 164 (38). HRMS Calcd for $C_{19}H_{15}NO_5$, 337.0950; found, 337.0950.

Oxidation of 14c. Synthesis of 8,9-Dimethoxy-6,7-methylenedioxy-[1]benzoxepino[2,3,4-ij]isoquinolin-12-one (15c). Compound **14c** (200 mg, 0.59 mmol) was dissolved in anhydrous pyridine (2.5 ml) and the solution was refluxed under O_2 for 23h. After cooling, the solvent was concentrated and the residue was chromatographed (SiO_2, 95:5, CH_2Cl_2/MeOH) to afford 140 mg (67%) of **15c** as a yellow solid. IR ($CHCl_3$): 3010, 1670 (CO), 1600, 1570, 1500, 1455, 1295, 1105. ^{1}H NMR (ppm): 8.62 (d, J= 5.4, 1H, Ar-H), 7.65 (d, J= 5.4, 1H, Ar-H), 7.48 (d, J= 8.7, 1H, Ar-H), 7.01 (s, 1H, Ar-H), 6.83 (d, J= 8.7, 1H, Ar-H), 6.27 (s, 2H, OCH_2O), 4.06 (s, 3H, OMe), 3.92 (s, 3H, OMe). ^{13}C NMR (CF_3CO_2D, ppm): 179.3 (CO), 157.8(C), 149.0, (C), 142.3 (C), 141.4 (C), 138.1 (C), 137.8 (C), 132.0 (C), 129.6 (CH), 119.0 (C), 60.4 (OMe), 54.5 (OMe). MS: m/e (%) 351 (M^+, 55), 320 (37), 265 (25), 152 (30), 151 (51), 55 (100). HRMS Calcd for $C_{19}H_{13}NO_6$, 351.0742; found, 351.0742.

Reduction of 15c. Synthesis of 8,9-Dimethoxy-6,7-methylenedioxy-12H-[1]benzoxepino[2,3,4-ij]isoquinolin-12-ol (16). To a solution of 20 mg of **15c** in 2 ml of anhydrous CH_2Cl_2 under Ar was added solid $NaBH_4$ in small portions until analysis on silica gel showed no remaining ketone. The reaction mixture was poured into 3M NaOH and extracted with methylene chloride (2x15 ml). The organic layer was washed with water (10 ml) and dried (Na_2SO_4) and the solvent was evaporated. The residue was subjected to preparative tlc (98:2, CH_2Cl_2/MeOH) to afford two products, the less polar of which was identified as **16**. IR ($CHCl_3$): 3300, 3010, 2940, 1500, 1455, 1275, 1200. ^{1}H NMR (CD_3CN, ppm): 8.20 (d, J= 5.7, 1H, Ar-H), 7.53 (d, J=5.7, 1H, Ar-H), 7.32 (d, J=8.6, 1H, Ar-H), 7.07 (s, 1H, Ar-H), 6.88 (d, J= 8.6, 1H, Ar-H), 6.47 (s, 1H, CH), 6.24 (s, 2H, OCH_2O), 6.13 (s, 1H, OH), 3.87 (s, 3H, OMe), 3.81 (s,

3H, OMe). ^{13}C NMR (ppm): 154.6, 152.9(C), 152.3, (C), 147.7 (C), 142.7 (C), 141.3 (C), 138.9 (CH), 135.8 (C), 135.5 (C), 130.3 (C), 120.5 (CH), 118.6 (CH), 117.6 (C), 109.3 (CH), 102.6 (CH_2), 99.6 (CH), 69.2 (CH), 61.8 (OMe), 56.3 (OMe). MS: m/e (%) 353 (M^+, 57), 352 (36), 324 (100), 322 (31), 308 (26), 280 (14). UV ($CHCl_3$) 284, 320, 332.

Preparation of O-methyloxime of 10,11-Dihydro-2,3,6-trimethoxy-dibenz(b,f)oxepin-10-one (17) . 650 mg (2.16 mmol) of **11a**, 550 mg (6.58 mmol) of O-methyl hydroxilamine hydrochloride and 2.5 ml of pyridine were dissolved in 50 ml of absolute ethanol and the solution was refluxed for 2h. After concentration of the solvent, the residue was dissolved in 25 ml of methylene chloride and washed with 5% HCl (2x10 ml) and brine (1x10 ml). Filtration through SiO_2 (1:3, EtOAc/Hexane) afforded 630 mg (89%) of **17** as a pale yellow solid, mp 147-148°C (MeOH). IR ($CHCl_3$): 3020-2940, 1510, 1440, 1265, 1115, 1050. ^1H NMR (ppm): 7.44 (dd, J=8.0 and 1.6, 1H, Ar-H), 7.01 (t, J=8.0, 1H, Ar-H), 6.93 (dd, J=8.0 and 1.6, 1H, Ar-H), 6.88 (s, 1H, Ar-H), 6.73 (s, 1H, Ar-H), 4.07 (s, 2H, Ar-CH_2), 4.02 (s, 3H, OMe), 3.95 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.84 (s, 3H, OMe). ^{13}C NMR (ppm): 152.2 (C), 151.9 (C), 151.4 (C), 148.3 (C), 147.0 (C), 146.5 (C), 126.8 (C), 123.6 (CH), 120.1 (C), 119.4 (CH), 112.8 (CH), 112.4 (CH), 105.4 (CH), 62.0 (OMe), 56.3 (OMe), 56.2 (OMe), 56.1 (OMe), 30.1 (CH_2). MS: m/e (%) 329 (M^+, 57), 282 (50), 266 (100), 254 (25), 167 (44). Anal. Calcd for $C_{18}H_{19}NO_5$, C 65.64, H 5.81, N 4.25; found, C 65.29, H 5.75, N 4.15.

N-formyl, 10-amino-10,11-dihydro-2,3,6-trimethoxy-dibenz(b,f)oxepine (18). 4 ml (4.0 mmol) of borane in THF was added at 0°C to a solution of 240 mg (0.73 mmol) of **17** in 8 ml of anhydrous THF, and the resulting mixture was refluxed under Ar for 15h. After cooling, 7 ml of H_2O and 7 ml of 20% KOH were sequentially added and the mixture was again refluxed for 1h before being poured into water and extracted with methylene chloride (2x20 ml). The organic phase was extracted with 10% HCl (5x15 ml) and the aqueous layer was basified with 10% KOH and extracted with methylene chloride (4x15 ml). The organic extracts were dried (Na_2SO_4) and the solvent was evaporated, affording a white solid which was stirred with 15 ml of acetic-formic anhydride[20] for 3h before being cooled, basified with 10% NaOH and extracted with methylene chloride (2x20 ml). The organic phase was washed with 5% HCl (2x20 ml) and water (1x10 ml) and dried (Na_2SO_4). After evaporation of the solvent 190 mg (81%) of **18** was obtained as a white solid, mp: 193-194°C (MeOH). IR ($CHCl_3$): 3420, 3020, 2960, 2940, 1675, 1510, 1465, 1440. ^1H NMR (ppm): 8.17 (s, 1H, CHO), 7.04 (t, J= 7.7, 1H, Ar-H), 6.90-6.85 (m, 3H, 3xAr-H), 6.61 (s, 1H, Ar-H), 6.26 (d, J= 9.1, NH), 5.59 (m, 1H, NCH), 3.92 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.39 (dd, J= 15.2 and 3.2, 1H, Ar-CH), 3.16 (dd, J= 15.2 and 5.5, 1H, Ar-CH). ^{13}C NMR (ppm): 160.2 (CO), 151.5 (C), 150.2 (C), 148.3 (C), 146.5 (C), 146.0 (C), 132.0 (C), 124.5 (CH), 121.7 (CH), 119.3 (C), 113.4 (CH), 111.7 (CH), 105.6 (CH), 56.3 (OMe), 56.1 (OMe), 56.0 (OMe), 48.3 (CH), 35.5 (CH_2). MS: m/e (%) 329 (M^+, 4), 284 (100), 241 (28), 139 (21). Anal. Calcd for $C_{18}H_{19}NO_5$, C 65.64, H 5.81, N 4.25; found, C 65.77, H 5.68, N 4.01.

10-N-methylamine-10,11-dihydro-2,3,6-trimethoxy-dibenz(b,f)oxepine (19). To a suspension of 80 mg (2.1 mmol) of LAH in 10 ml of anhydrous THF cooled at 4°C was slowly added a solution of 160 mg (0.48 mmol) of **18** in 10 ml of anhydrous THF. The mixture was refluxed for 4h and

cooled. 0.08 ml of H_2O, 0.08 ml of 15% NaOH and 0.24 ml of H_2O were sequentially added, the resulting paste was filtered and the solid was washed with ether. After evaporation of the organic solvents, the residue was dissolved in 20 ml of methylene chloride, washed with brine (1x10 ml) and dried (Na_2SO_4) and the methylene chloride was evaporated to afford 120 mg (74%) of **19** as an oil. IR ($CHCl_3$): 3150, 3030, 2970, 2950, 1515, 1470, 1200. ^1H NMR (ppm): 7.07 (t, J= 7.8, 1H, Ar-H), 6.91-6.84 (m, 3H, 3xAr-H), 6.56 (s, 1H, Ar-H), 4.18 (dd, J= 7.3 and 3.5, 1H, NCH), 3.90 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.31 (dd, J= 15.7 and 3.5, 1H, Ar-CH), 3.09 (dd, J= 15.7 and 7.3, 1H, Ar-CH), 2.48 (s, 3H, NMe). MS: m/e (%) 315 (M^+, 97), 300 (100), 285 (22), 284 (58), 269 (60). HRMS Calcd for $C_{18}H_{21}NO_4$, 315.1470; found, 315.1470.

10-(N-methylamino acetaldehyde diethyl acetal)-10,11-dihydro-2,3,6-trimethoxy -dibenz(b,f)oxepine (20). 100 mg (0.31 mmol) of **19**, 0.5 ml (3.3 mmol) of bromoacetaldehyde diethyl acetal and 300 mg (3.5 mmol) of sodium bicarbonate were heated at 130°C under Ar for 4h. After cooling, the mixture was concentrated under reduced pressure and the residue was dissolved in 15 ml of ether, washed with water (2x10 ml) and dried (Na_2SO_4). The organic solvent was evaporated and the crude was filtered through SiO_2 (97:3, CH_2Cl_2/MeOH), affording 120 mg (91%) of **20** as an oil. IR ($CHCl_3$): 3020-2950, 1510, 1465, 1260, 1200, 1115. ^1H NMR (ppm): 7.25 (d, J= 7.9, 1H, Ar-H), 6.98 (t, J= 7.9, 1H, Ar-H), 6.80 (s, 1H, Ar-H), 6.79 (d, J= 7.9, 1H, Ar-H), 6.67 (s, 1H, Ar-H), 4.57 (t, J= 5.0, 1H, C<u>H</u>(OEt)$_2$), 3.96 (m, 1H, NCH), 3.92 (s, 3H, OMe), 3.84 (s, 6H, 2xOMe), 3.73-3.40 (m, 5H, 2xOCH_2, ArCH), 2.87 (m, 1H, ArCH), 2.77 (d, J= 5.0, 2H, NCH_2), 2.38 (s, 3H, NMe), 1.21 (t, J= 7.0, 3H, CH_3), 1.18 (t, J= 7.0, 3H, CH_3). ^{13}C NMR (ppm): 152.1 (C), 151.1 (C), 147.5 (C), 146.8 (C), 145.7 (C), 133.1 (C), 123.0 (2xCH), 122.3 (C), 112.4 (CH), 110.2 (CH), 105.1 (CH), 102.3 (CH), 64.0 (CH), 61.8 (O-CH_2), 61.5 (O-CH_2), 56.5 (N-CH_2), 56.1 (OMe), 55.9 (OMe), 55.8 (OMe), 38.6 (NMe), 28.8 (Ar-CH_2), 15.0 (2xCH_3). MS: m/e (%) 431 (M^+, 7), 386 (3), 328 (14), 286 (33), 285 (100). HRMS Calcd for $C_{24}H_{33}NO_6$, 431.2307; found, 431.2307.

Acid cyclisation of 20. Obtainment of the epimeric mixture of O-methyllimousamine (21). 100 mg (0.23 mmol) of **20** was dissolved in 2 ml of 6N HCl and the solution was stirred at room temperature for 16h under Ar. After basification, the aqueous phase was extracted with methylene chloride (2x15 ml) and the organic extract was washed with H_2O (10 ml) and dried (Na_2SO_4). Evaporation of the solvent afforded **21** as an oil in almost quantitative yield (80 mg). MS: m/e (%) 357 (M^+, 32), 342 (100), 324 (14). This oil was identified by tlc comparison with an authentic sample.[13]

Synthesis of 6,9,10-Trimethoxy-1-methyl-1H-[1]benzoxepino[2,3,4-ij]isoquinoline-2,3-dione (dioxocularine, 22). 0.05 g (0.14 mmol) of the epimeric mixture of **21** was dissolved in 15 ml of anhydrous benzene and Ar was bubbled through this solution for 30 min. 0.08 g (0.35 mmol) of DDQ was added and the mixture was refluxed for 2h.[14] After cooling and evaporation of the solvent, the residue was chromatographed (Al_2O_3 grade III, CH_2Cl_2), affording 20 mg (35%) of **22** as a yellow solid which was crystallized from ethanol, mp: 212-214°C (lit 212-214°C).[15] ^1H NMR (ppm): 8.04 (d, J= 8.7, 1H, Ar-H), 7.19 (d, J= 8.7, 1H, Ar-H), 6.91 (s, 1H, Ar-H), 6.69 (s, 1H, Ar-H), 6.64 (s, 1H, C=CH), 4.06 (s, 3H, OMe), 3.93 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.67 (s, 3H, NMe). Identified by tlc comparison with an authentic sample.[15]

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