A Synthetic Route to (±)-Clavizepine through a Dibenzoxepine Intermediate†

M. C. de la Fuente, Luis Castedo,* and Domingo Domínguez*

Departamento de Química Orgánica, Facultad de Química, Universidad de Santiago y Sección de Alcaloides del CSIC, 15706 Santiago de Compostela, Spain

Received February 13, 1996⊗

A new synthesis of (±)-clavizepine (**1a**), based on the dibenzoxepinediol **10** as main intermediate is described. The key step is the contraction of the oxepine ring to give the xanthene-9-carboxyaldehyde **11**, on which the nitrogenated ring can be readily assembled.

Introduction

(−)-Clavizepine (**1a**) is the sole member of a unique class of alkaloids known as the dibenzopyranazepines. First described in 1986,[1] it has recently been synthesized by two independent procedures, both of which employ a xanthene-9-carboxylate as the key intermediate.[2] Here we describe an alternative approach in which the key step is the ring contraction of a dibenzoxepinediol derivative to a xanthene-9-carboxaldehyde (Scheme 1).

We have previously demonstrated the versatility of dibenzoxepinones as intermediates for the synthesis of both cularine alkaloids[3] and the dibenzopyranazepine skeleton (*O*-methylclavizepine (**1b**) can be prepared in 21% overall yield from dibenzoxepinone **3b** in just nine steps).[4]

However, application of this method to the synthesis of natural clavizepine (**1a**) was hampered by difficulties in the preparation of the required dibenzoxepinone precursor, **3c**. PPA failed to achieve intramolecular acylation of 2-[2-(benzyloxy)phenoxy]-4,5-dimethoxyphenylacetic acid,[5] and McLean's indirect procedure[6] (involving the morpholinamide of the acid) led to only 14% yield.

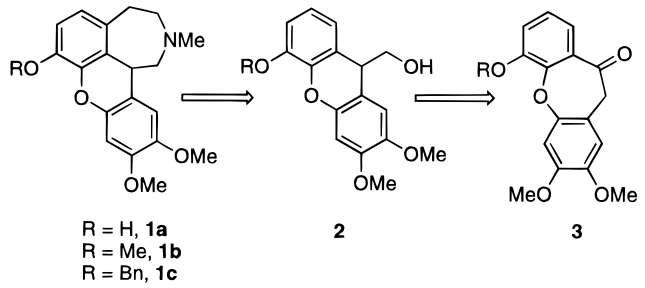
Because of the above difficulties, we approached the preparation of 2-(benzyloxy)-4,5-dimethoxydibenzoxepinone (**3c**) by an alternative method based on alkylation of the anion of an appropriate 1,3-dithiane with the corresponding benzylic halide (Scheme 2).[7] Although this procedure, too, failed to afford **3c** (*vide infra*), it turned out to provide a new route to the dibenzoxepine **9c**, which in turn proved to be a suitable intermediate for synthesis of clavizepine.

Results and Discussion

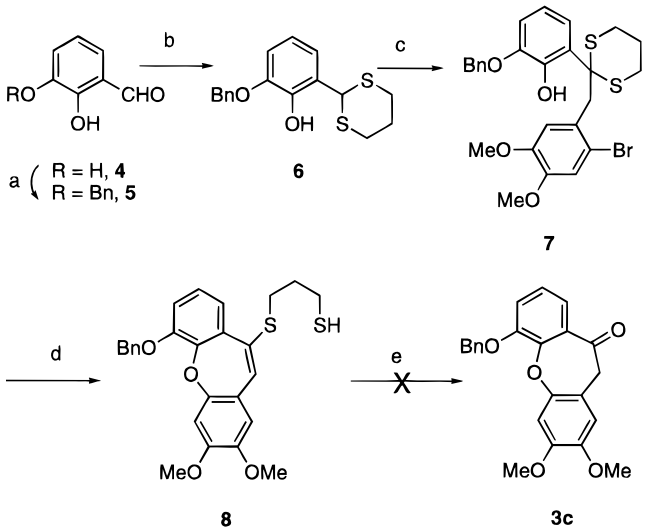
2,3-Dihydroxybenzaldehyde (**4**) was selectively benzylated at the hydroxyl *meta* to the aldehyde by treatment with 2 equiv of NaH followed by addition of benzyl chloride.[8] Treatment of the aldehyde **5** with 1,3-propanedithiol under Lewis acid catalysis led to the dithioketal **6**.

Although in previous work[7] we protected the phenolic hydroxyl prior to alkylation we now found that alkylation can be successfully carried out on the dianion derivative of **6**: after treatment of the phenolic dithioketal **6** with 2 equiv of *n*-BuLi, the resulting dianion was alkylated with 2-bromo-4,5-dimethoxybenzyl bromide, giving the coupled product **7** in 74% yield.

Scheme 1



Scheme 2



Reagents: (a) (i) NaH (2eq), DMSO; (ii) Benzyl chloride, 59%; (b) 1,3-Propanedithiol, $BF_3{\cdot}OEt_2$, $CHCl_3$, 93%; (c) (i) *n*-BuLi, THF; (ii) 2-Bromo-4,5-dimethoxybenzyl bromide, 74%; (d) CuO, K_2CO_3, py; (e) HCl, CH_3CN, glyoxylic acid.

† Dedicated to the memory of J. M. Boente.

⊗ Abstract published in *Advance ACS Abstracts,* July 15, 1996.

(1) Boente, J. M.; Castedo, L.; Domínguez, D.; Ferro. M. C. *Tetrahedron Lett*. **1986**, *34*, 4077.

(2) (a) Ishibashi, H.; Takagaki, K.; Imada, N.; Ikeda, M. *Synlett* **1994**, 49. (b) Ishibashi, H.; Takagaki, K.; Imada, N.; Ikeda, M. *Tetrahedron* **1994**, *50*, 10215. c) Vázquez, R.; de la Fuente, M. C.; Castedo, L.; Domínguez, D. *Synlett* **1994**, 433.

(3) (a) Lamas, C.; Castedo, L.; Domínguez, D. *Tetrahedron Lett*. **1990**, *31*, 6247. b) García, A.; Castedo, L.; Domínguez, D. *Tetrahedron Lett*. **1993**, *34*, 1797. c) García, A.; Castedo, L.; Domínguez, D. *Tetrahedron* **1995**, *51*, 8585.

(4) de la Fuente, M. C.; Castedo, L.; Domínguez, D. *Tetrahedron* **1996**, *52*, 4917.

(5) Kametani, T.; Fukumoto, K.; Nakano, T. *Yakugaku Zasshi* **1962**, *82*, 1307. *Chem. Abstr.* **1963**, *58*, 13913h.

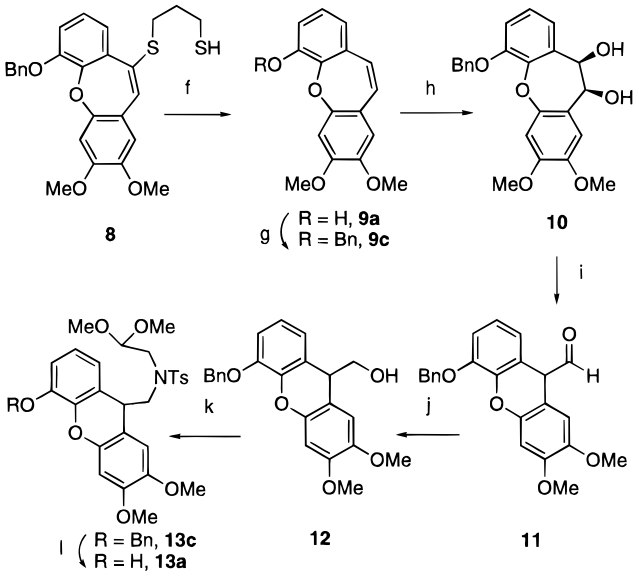
(6) Noguchi, I,; McLean, D. *Can. J. Chem*. **1975**, *53*, 125.

(7) Lamas, C.; García, A.; Castedo, L.; Domínguez, D. *Tetrahedron Lett.* **1989**, *30*, 6927.

(8) (a) Kessar, S. V.; Gupta, Y. P.; Mohammad, T.; Goyal, M.; Sawal, K. K. *J. Chem. Commun.* **1983**, 400. (b) Kessar, S. V.; Gupta, Y. P.; Balakrishnan, P.; Sawal, K. K.; Mohammad, T.; Dutt, M. *J. Org. Chem.* **1988**, *53*, 1708.

S0022-3263(96)00291-5 CCC: $12.00

Scheme 3[a]



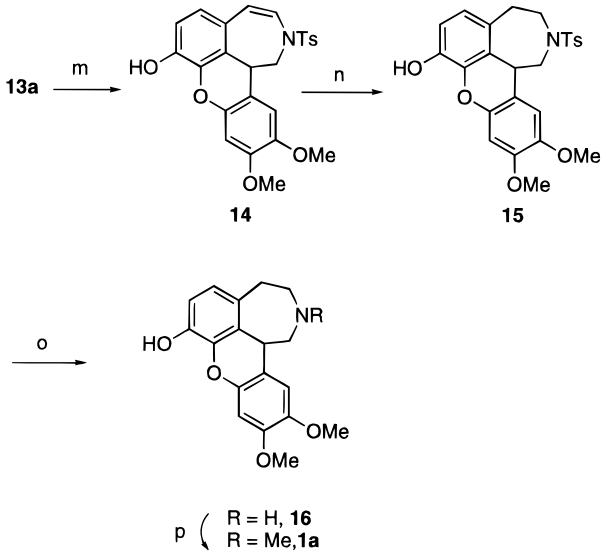
[a] Reagents: (f) Raney Ni, acetone, 68% of **9c** and 14% of **9a** starting from **7**; (g) (i) NaH, DMF; (ii) benzyl chloride, 84%; (h) OsO_4, NMMO, THF, 82%; (i) H_2SO_4, AcOH, 96%; (j) $NaBH_4$, MeOH, 98%; (k) *N*-tosyl AADA, Ph_3P, DEAD, THF, 52%; (l) H_2, Pd/C 10%, CH_2Cl_2, MeOH, 87%.

Ullmann reaction of bromophenol **7** afforded a mixture that TLC showed to contain two main products of very similar Rf, which were highly fluorescent when excited at 360 nm. Purification by column chromatography led to a 2:1 mixture of the two fluorescent compounds, as determined by ^{1}H NMR. The GC/MS of this mixture showed the molecular ion of the major compound at *m/e* 466 (53%), corresponding to the dibenzoxepine structure **8** which results from β-elimination of the dithioacetal following the Ullmann reaction. The minor compound has very similar ^{1}H and ^{13}C NMR data and an MS peak (24%) at 465, which suggests a disulfide structure derived from the oxidation of **8**, but this structure could not be firmly established.

Despite previous results,[7] hydrolysis of the crude mixture from the Ullmann reaction with acetonitrile/concd HCl in the presence of glyoxylic acid, instead of affording **3c**, produced a complex mixture of products. However, reduction of the mixture of fluorescent compounds with Raney nickel gave the alkenes **9c** (in 68% yield) and **9a** (in 14% yield); see Scheme 3. Alkene **9a** was reprotected, in 84% yield, by treatment with NaH followed by addition of benzyl chloride.

Alkene **9c** was hydroxylated in 82% yield by OsO_4/NMMO in aqueous THF. Pinacol rearrangement of diol **10** in AcOH/H_2SO_4 afforded a 96% yield of the aldehyde **11**, which was reduced with $NaBH_4$ in methanol to give alcohol **12** in 98% yield. Mitsunobu reaction[9] of **12** with *N*-tosyl aminoacetaldehyde dimethyl acetal gave dimethylacetal **13c** in 52% yield,[10] and debenzylation of **13c** by catalytic hydrogenation gave the phenolic compound **13a** in 87% yield. Treatment of a solution of **13a** in acetic acid with HCl at 75 °C afforded the cyclic compound **14** in 79% yield. Catalytic hydrogenation of **14** gave a 92% yield of **15**, which by reductive cleavage of the sulfonamide and *N*-methylation of the resulting amine (**16**) gave a product with IR, MS, ^{1}H NMR and ^{13}C NMR spectra that were identical to those of the natural compound (Scheme 4).

Scheme 4



Reagents: (m) HCl, AcOH, 79 %; (n) H_2, Pd/C 10%, $CHCl_3$, 92 %; (o) Na/Hg, Na_2HPO_4, MeOH, 73 %; (p) H_2CO, HCO_2H, 90 %.

The total synthesis of (±)-clavizepine (**1a**) was accomplished from the key dibenzoxepine **9c** in nine steps and 17% overall yield.

Experimental Section

General Procedures. Solvents were dried by distillation from a drying agent:[11] THF and benzene from Na/benzophenone; pyridine, Et_3N and diisopropylamine from CaH_2. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 250.13 and 62.83 MHz in $CDCl_3$. LR and HR mass spectra were recorded at 70 eV. Plate chromatography was performed on Merck silica gel 60 F_{254} and visualized with UV light (254 and 360 nm) or iodine vapor. Flash column chromatography was performed on Merck silica gel 60 (230−240 mesh ASTM).

2-[3-(Benzyloxy)-2-Hydroxyphenyl]-1,3-dithiane (6). To a solution of 3-(benzyloxy)-2-hydroxybenzaldehyde[8] (14.1 g, 61.7 mmol) in dry chloroform (90 mL) were added 1,3-propanedithiol (6.5 mL, 65 mmol), anhydrous Na_2SO_4 (5 g), and $BF_3{\cdot}OEt_2$ (3.8 mL, 30 mmol). The mixture was stirred at rt for 2 h and then filtered, and the filtrate was washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was recrystallized twice from CH_2Cl_2/*n*-hexane to afford compound **6** (18.4 g, 93%). Mp: 136−138 °C. IR (NaCl) 3510 (OH), 2900, 1610, 1590, 1475, 1385, 1355, 1270, 1050, 910 cm^{-1}; ^{1}H NMR δ 7.47−7.35 (m, 5H), 7.20 (dd, J = 3.1 and 6.0 Hz, 1H), 6.88−6.84 (m, 2H), 6.03 (s, 1H), 5.70 (s, 1H), 5.10 (s, 2H), 3.14 (td, J = 14.7 and 2.4 Hz, 2H), 2.98−2.87 (m, 2H), 2.22−214 (m, 1H), 2.02−1.92 (m, 1H); ^{13}C NMR δ 145.83, 142.64, 136.47, 129.02 (CH × 2), 128.70 (C), 128.09 (CH × 2), 125.16, 121.15 (CH), 120.42 (CH), 112.15 (CH), 71.53 (CH_2), 44.27 (CH), 32.54 (CH_2 × 2), 25.58 (CH_2). MS, *m/z* (%): 318 (M^+, 27), 227 (14), 196 (47), 153 (31), 91 (100). Anal. Calcd for $C_{17}H_{18}O_2S_2$: C 64.12, H 5.70. Found: C 63.90, H 5.56.

2-[3-(Benzyloxy)-2-hydroxyphenyl]-2-(2-bromo-4,5-dimethoxybenzyl)-1,3-dithiane (7). 1.6 M *n*-BuLi (39.25 mL, 62.8 mmol) was added to a cooled solution (−40 °C) of compound **6** (10 g, 31.4 mmol) in dry THF (120 mL). The

(9) García, A.; Castedo, L.; Domínguez, D. *Synlett* **1993**, 271.

(10) The main secondary product is 5-(benzyloxy)-2,3-dimethoxy-9-methylenexanthene, which is easily oxidized to 5-(benzyloxy)-2,3-dimethoxyxanthone during workup.

(11) Perrin, D. D.; Aramego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed.; Pergamon: Oxford, 1988.

solution was warmed gradually to 0 °C, and a solution of 2-bromo-4,5-dimethoxybenzyl bromide (9.73 g, 31.4 mmol) in THF (32 mL) was added. The mixture was stirred at rt for 8 h and then neutralized by dropwise addition of 10% HCl. The solvent was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. This final residue was purified by column chromatography (silica gel; 1:1 CH_2Cl_2/hexane) to afford dithiane **7**, which was recrystallized from ether (12.7 g, 74%). Mp: 135−137 °C. IR (NaCl) 3150 (OH), 1570, 1510, 1450, 1350, 1260, 1165, 1030, 740 cm^{-1}; ^1H NMR δ 8.73 (s, 1H), 7.49−7.40 (m, 2H), 7.38−7.31 (m, 2H), 7.27−7.24 (m, 2H), 6.96−6.94 (m, 1H), 6.94 (s, 1H), 6.73 (t, 1H, J = 8.1), 5.94 (s, 1H), 5.16 (s, 2H), 3.80 (s, 3H), 3.59 (s, 2H), 3.36 (s, 3H), 2.94−2.81 (m, 2H), 2.76−2.67 (m, 2H), 2.00−1.94 (m, 2H); ^{13}C NMR δ 147.86, 147.81, 146.57, 146.14, 136.49, 128.05 (CH × 2), 127.42 (CH), 126.86 (CH × 2), 125.36, 125.02 (CH), 123.09, 118.46 (CH), 115.61, 114.30 (CH), 114.15 (CH), 114.06 (CH), 71.66 (CH_2), 59.86, 56.17 (OMe), 55.58 (OMe), 45.43 (CH_2), 28.26 (CH_2 × 2), 24.50 (CH_2); MS (FAB), *m*/*z* (%): 549 (3), 548 (3), 547 (M + 1,11), 546 (3), 545 (9), 351 (12), 317 (11), 229 (27), 151 (100). Anal. Calcd for $C_{26}H_{27}O_4S_2Br$, C 57.03, H 4.97. Found: C 57.00, H 4.87.

Ullmann Reaction of Bromophenol 7 To Obtain Compound 8. Phenol **7** (1.4 g, 2.5 mmol), CuO (1 g, 12.6 mmol), anhydrous K_2CO_3 (2 g, 14.4 mmol), and dry deaerated pyridine (10 mL) were mixed and then refluxed under Ar for 1 h. After cooling, the reaction mixture was filtered through Celite, and the filtrate was washed with 10% HCl and water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was column-chromatographed (silica gel, 2:1 CH_2Cl_2/hexane) to afford a main fraction (1 g) consisting of a mixture of two compounds with very similar R_f, both of which fluoresced under the 360 nm lamp. The ^1H NMR spectrum shows a 2:1 mixture of dibenzoxepine **8** and an unknown compound.

^1H NMR: **major compound** (**8**), δ 7.54−7.51 (m, 2H), 7.41−7.33 (m, 4H), 7.08−6.98 (m, 3H), 6.82 (s, 1H), 6.62 (s, 1H), 5.16 (s, 2H, OCH_2Bn), 3.81 (s, 3H, OMe), 3.70 (s, 3H, OMe), 2.84−2.73 (m, 4H), 1.99 (q, J = 6.8 Hz, 2H); **minor compound**, δ 7.54−7.51 (m, 2H), 7.41−7.33 (m, 4H), 7.08−6.98 (m, 3H), 6.79 (s, 1H), 6.59 (s, 1H), 5.14 (s, 2H, OCH_2Bn), 3.78 (s, 3H, OMe), 3.69 (s, 3H, OMe), 2.84−2.73 (m, 4H), 1.99 (q, J = 6.8 Hz, 2H). GC/MS, **major compound** (**8**), *m*/*z* (%) 466 (M^+, 54), 433 (11), 432 (16), 392 (15), 348 (20), 347 (80), 301 (12), 257 (58), 256 (48), 229 (12), 228 (21), 91 (100); **minor compound**, *m*/*z* (%) 465 (24), 464 (42), 392 (14), 301 (17), 149 (15), 91 (100).

Preparation of Dibenzoxepines 9a and 9c. Compound **7** (11.8 g, 21.6 mmol), CuO (9.07 g, 114 mmol), anhydrous K_2CO_3 (18.14 g, 131 mmol), and dry deaerated pyridine (63 mL) were mixed and then refluxed under Ar for 1 h. After cooling, the reaction mixture was filtered through Celite, and the filtrate was washed with 10% HCl and water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue (a 2:1 mixture of **8** and an unknown compound) was dissolved in acetone (100 mL) under argon, treated with Raney nickel (90 g, 50% slurry in water), and then heated at 70 °C for 3 h. The cooled reaction mixture was filtered through Celite and concentrated in vacuo, and the residue was dissolved in CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated in vacuo. This final residue was purified by column chromatography (silica gel; 2:1 CH_2Cl_2/hexane) to afford alkenes **9c** (5.3 g, 68%) and **9a** (0.8 g, 14%).

6-Hydroxy-2,3-dimethoxydibenzoxepine (9a). Recrystallized from EtOAc/*n*-hexane, mp 148−151 °C. IR (KBr) 3460 (OH), 1610, 1520, 1460, 1350, 1240, 1210, 1170, 1100, 1000, 860, 800 cm^{-1}. ^1H NMR δ 6.99−6.95 (m, 2H), 6.70 (s, 1H), 6.67−6.64 (m, 1H), 6.60−6.58 (m, 3H), 6.25 (s, 1H, OH), 3.83 (s, 3H), 3.81 (s, 3H); ^{13}C NMR δ 150.46, 150.36, 147.79, 146.46, 144.34, 130.94, 129.96 (CH), 128.81 (CH), 125.50 (CH), 122.26, 120.82 (CH), 116.02 (CH), 111.81 (CH), 105.37 (CH), 56.51 (OMe), 56.38 (OMe); MS, *m*/*z* (%): 270 (M^+, 100), 255 (11), 227 (8), 199 (7), 181 (9), 149 (8), 83 (8). Anal. Calcd for $C_{16}H_{14}O_4$: C 71.10, H 5.22. Found: C 70.86, H 5.33.

6-(Benzyloxy)-2,3 dimethoxydibenzoxepine (9c). Recrystallized from EtOAc/*n*-hexane, mp 102−104 °C. IR (NaCl) 1610, 1570, 1510, 1260, 1210, 1110, 1000, 860, 800, 730, 700 cm^{-1}. ^1H NMR δ 7.53 (d, J = 6.8 Hz, 2H), 7.41−7.32 (m, 3H), 6.94−7.03 (m, 2H), 6.83 (s, 1H), 6.77 (dd, J = 7.3 and 1.8 Hz, 1H), 6.69 (s, 2H), 6.64 (s, 1H), 5.16 (s, 2H), 3.83 (s, 3H), 3.75 (s, 3H); ^{13}C NMR δ 151.24, 151.12, 150.56, 146.15, 145.56, 137.42, 132.53, 130.16 (CH), 128.81 (CH × 2), 128.64 (CH), 128.24 (CH), 127.68 (CH × 2), 124.90 (CH), 122.65 (C), 121.19 (CH), 114.22 (CH), 111.01 (CH), 105.96 (CH), 71.10 (CH_2), 56.50 (OMe), 56.13 (OMe). MS, *m*/*z* (%): 360 (M^+, 94), 241 (21), 225 (13), 195 (22), 91 (100). Anal. Calcd for $C_{23}H_{20}O_4$: C 76.65, H 5.59. Found: C 76.29, H 5.89.

***O*-Benzylation of 6-Hydroxy-2,3 dimethoxybenzoxepine (9a).** NaH (80% dispersion in mineral oil, 266 mg, 8.8 mmol) was washed twice with dry THF (3 mL), and then dry DMF was added followed by a solution of compound **9a** (0.8 g, 2.96 mmol) in DMF (7 mL). The mixture was stirred for 1 h, and benzyl chloride (0.5 mL, 2.96 mmol) was added. After stirring for 18 h at rt, the solution was quenched with water, diluted with CH_2Cl_2, and washed with water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Recrystallization of the residue from ether/*n*-hexane afforded alkene **9c** (1.07 g, 84%).

Hydroxylation of 9c. To a solution of compound **9c** (5.21 g, 14 mmol) in THF (52 mL) were added *N*-methylmorpholine *N*-oxide monohydrate (2 g, 14.3 mmol) and 26 mL of a 5.6 × 10^{-3} M solution of OsO_4 (0.14 mmol). The mixture was stirred overnight at rt and then poured into an ice cooled mixture of 10% HCl and 15% sodium bisulfite (5:1, v/v). This solution was extracted with EtOAc, and the extract was washed with water, dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo. Recrystallization of the residue from EtOAc/*n*-hexane afforded diol **10** (4.69 g, 82%). Chromatography of the mother liquors (silica gel, CH_2Cl_2) gave 169 mg of 6-(benzyloxy)-2,3-dimethoxydibenzoxepine-10,11-dione (3% yield).

6-(Benzyloxy)-10,11-dihydro-2,3-dimethoxydibenzoxepine-10,11-diol (10). Mp: 161−163 °C. IR (KBr) 3480 (OH), 3320 (OH), 1610, 1510, 1200, 860, 755, 730, 695 cm^{-1}. ^1H NMR δ 7.49−7.46 (m, 2H), 7.40−7.35 (m, 3H), 7.10−7.08 (m, 2H), 6.93−6.90 (m, 2H), 6.76 (s, 1H), 5.35−5.33 (m, 1H), 5.14 (d, J = 11.6 Hz, 1H), 5.08 (d, J = 11.6 Hz, 1H), 4.96−4.93 (m, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.04 (d, J = 8.9 Hz, 1H), 2.24 (d, J = 9.4 Hz, 1H). ^{13}C NMR δ (DMSO-d_6): 149.40, 148.27, 147.99, 145.03, 143.87, 137.43, 135.53, 128.43 (CH × 2), 127.81 (CH), 127.31 (CH × 2), 123.93 (CH), 122.49, 120.37 (CH), 114.47 (CH), 112.50 (CH), 104.45 (CH), 71.71 (CH), 70.03 (CH), 69.97 (CH_2), 55.87 (OMe), 55.36 (OMe). MS, *m*/*z* (%): 394 (M^+, 24), 347 (30), 285 (96), 269 (34), 257 (53), 229 (9), 91 (100). Anal. Calcd for $C_{23}H_{22}O_6$: C 70.04, H 5.62. Found: C 69.75, H 5.58.

6-(Benzyloxy)-2,3-dimethoxydibenzoxepine-10,11-dione. Recrystallized from EtOAc/*n*-hexane. Mp: 173−175 °C. IR (NaCl) 1690, 1660, 1600, 1510, 1450, 1410, 1270 cm^{-1}. ^1H NMR δ 7.50 (d, J = 6.8 Hz, 2H), 7.43−7.32 (m, 5H), 7.19 (s, 1H), 7.17−7.15 (m, 1H), 6.83 (s, 1H), 5.18 (s, 2H), 3.89 (s, 3H), 3.86 (s, 3H). ^{13}C NMR δ 188.39 (CO), 183.30 (CO), 156.05, 155.10, 150.54, 147.04, 147.00, 136.60, 130.15, 128.93 (CH × 2), 128.57 (CH), 127.60 (CH × 2), 126.27 (CH), 122.55 (CH), 118.94 (CH), 118.49, 111.16 (CH), 104.65 (CH), 71.56 (CH_2), 56.68 (OMe), 56.67 (OMe). MS, *m*/*z* (%): 390 (M^+, 17), 375 (7), 360 (13), 299 (13), 283 (43), 243 (22), 91 (100). Anal. Calcd for $C_{23}H_{18}O_6$: C 70.76, H 4.65. Found: C 70.88, H 4.96.

5-(Benzyloxy)-2,3-dimethoxyxanthene-9-carboxaldehyde (11). Diol **10** (3 g, 7.6 mmol) was dissolved in glacial acetic acid (78 mL), the solution was deaerated by bubbling argon through it, and three drops of concd H_2SO_4 were added. This mixture was stirred for 3 min at rt, diluted with water, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 5% K_2CO_3 solution and then with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Aldehyde **11** (2.75 g, 96%) was obtained as a foam that would not crystallize. IR (NaCl) 1720 (CHO), 1610, 1510, 1270, 1215, 1010, 735, 695 cm^{-1}. ^1H NMR δ 9.44 (d, J = 3.9 Hz, 1H), 7.50 (d, J = 7.3 Hz, 2H), 7.44−7.33 (m, 3H), 6.98−6.92 (m, 2H), 6.80 (s, 1H), 6.77 (dd, J = 7.1 and 2.1 Hz, 1H), 6.60 (s, 1H), 5.21 (s, 2H), 4.68 (d, J = 3.9 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H). ^{13}C NMR δ 194.97

(CHO), 149.59, 147.10, 145.22, 144.54, 141.02, 136.39, 128.08 (CH × 2), 127.53 (CH), 127.04 (CH × 2), 122.53 (CH), 120.98 (CH), 115.56, 113.47 (CH), 110.39 (CH), 104.74, 100.88 (CH), 70.56 (CH_2), 55.65 (OMe), 55.36 (OMe), 51.25 (CH). MS, (FAB), *m*/*z* (%): 377 (M + 1, 17), 376 (38), 375 (82), 363 (46), 347 (100).

5-(Benzyloxy)-9-(hydroxymethyl)-2,3-dimethoxyxanthene (12). To a solution of aldehyde **11** (2.75 g, 7.3 mmol) in methanol (160 mL), $NaBH_4$ (excess) was carefully added in small portions until no starting material could be detected by TLC. A 10% solution of HCl was slowly added until the reaction mixture was neutral, and then the methanol was removed in vacuo. The residue was extracted with CH_2Cl_2, and this solution was washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford 2.70 g of alcohol **12** (98% yield), which was recrystallized from ether. Mp: 108 °C. IR (NaCl) 3500 (OH), 1610, 1580, 1510, 1415, 1270, 1220, 1120, 910, 860 cm^{-1}; ^1H NMR δ 7.48 (d, J = 7.2 Hz, 2H), 7.40−7.31 (m, 3H), 6.94 (dd, J = 9.0 and 6.6 Hz, 1H), 6.85 (d, J = 7.2 Hz, 2H), 6.77 (s, 1H), 6.72 (s, 1H), 5.17 (s, 2H), 3.97 (t, J = 5.9 Hz, 1H), 3.88 (s, 6H), 3.69−3.65 (m, 2H), 2.02 (bs, 1H, OH); ^{13}C NMR δ 149.09, 147.28, 146.27, 145.46, 142.75, 137.31, 128.82 (CH × 2), 128.18 (CH), 127.64 (CH × 2), 123.15, 122.91 (CH), 121.45 (CH), 113.30 (CH), 112.50, 111.23 (CH), 101.35 (CH), 71.51 (CH_2), 69.26 (CH_2), 56.66 (OMe), 56.31 (OMe), 42.10 (CH). MS, *m*/*z* (%): 378 (M^+, 2), 348 (25), 347 (100), 256 (46), 228 (13). Anal calcd for $C_{23}H_{22}O_5$, C 73.00, H 5.86. Found: C 72.89, H 5.86.

Mitsunobu Reaction of Alcohol 12. Alcohol **12** (2.0 g, 5.28 mmol), *N*-tosyl aminoacetaldehyde dimethyl acetal (1.4 g, 5.4 mmol), and triphenylphosphine (1.45 g, 5.5 mmol) were dissolved in dry THF (80 mL) under argon. Diethyl azodicarboxylate (0.84 mL, 5.4 mmol) was added, and the mixture was stirred for 3 h at rt. The THF was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2, washed with 15% NaOH and then with brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded a residue which was column chromatographed (silica gel; 1:2 EtOAc/*n*-hexane) to give 9-methylene-2,3-dimethoxy-5-(benzyloxy)xanthene (0.62 g, 38%), 2,3-dimethoxy-5-(benzyloxy)xanthone (95 mg, 5%), and compound **13c** (1.69 g, 52%) as a foam.

***N*-(2,2-Dimethoxyethyl)-*N*-tosyl-9-(aminomethyl)-5-(benzyloxy)-2,3-dimethoxyxanthene (13c).** Crystallized from ether, Mp 145−148 °C. IR (NaCl) 1610, 1575, 1510, 1340, 1270, 1210, 1160, 1120, 1070, 910, 730 cm^{-1}. ^1H NMR δ 7.70 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 7.4 Hz, 2H), 7.41−7.35 (m, 3H), 7.27 (d, J = 8.0 Hz, 2H), 6.97−6.95 (m, 3H), 6.79 (s, 1H), 6.77 (s, 1H), 5.19 (s, 2H), 4.37 (t, J = 7.5 Hz, 1H), 4.03 (t, J = 4.9 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.45 (dd, J = 7.5 and 15.0 Hz, 1H), 3.33 (dd, J = 7.5 and 15.0 Hz, 1H), 3.13 (s, 3H), 3.12 (s, 3H), 3.03 (dd, J = 4.9 and 15.2 Hz, 1H), 2.85 (dd, J = 4.9 and 15.2 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR δ 148.81, 147.02, 145.91, 145.24, 143.35, 142.59, 137.17, 137.06, 129.56 (CH × 2), 128.46 (CH × 2), 127.81 (CH), 127.25 (CH × 2), 127.14 (CH × 2), 123.90, 122.74 (CH), 121.44 (CH), 113.25 (CH, C), 111.40 (CH), 103.32 (CH), 100.89 (CH), 71.28 (CH_2), 57.03 (CH_2), 56.22 (OMe), 55.92 (OMe), 54.23 (OMe × 2), 50.99 (CH_2), 39.14 (CH), 21.28 (Me). MS (FAB) *m*/*z* (%): 620 (M + 1, 1), 619 (3), 618 (2), 588 (4), 566 (5), 363 (20), 347 (100). Anal. Calcd for $C_{34}H_{37}O_8NS$: C 65.90, H 6.02, N 2.26. Found: C 66.20, H 6.07, N 1.96.

***N*-(2,2-Dimethoxyethyl)-*N*-tosyl-9-(aminomethyl)-2,3-dimethoxy-5-hydroxyxanthene (13a).** Compound **13c** (1.69 g, 2.73 mmol) and 10% Pd/C (150 mg) in MeOH (20 mL) and CH_2Cl_2 (20 mL) were stirred under 1 atm of H_2 for 1.5 h. After filtration through Celite and evaporation of the solvent in vacuo, sulfonamide **13a** was obtained and recrystallized from ether/*n*-hexane (1.25 g, 87%). Mp: 170−171 °C. IR (KBr) 3380 (OH), 1610, 1510, 1470, 1330, 1150, 1120, 1060, 1040, 1020, 960, 940, 850 cm^{-1}. ^1H NMR δ 7.70 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2, 2H), 6.95 (t, J = 7.9 Hz, 1H), 6.88 (dd, J = 1.6 and 7.9 Hz, 1H), 6.82 (s, 1H), 6.79 (dd, J = 7.9 and 1.6 Hz, 1H), 6.70 (s, 1H), 5.62 (bs, 1H, OH), 4.36 (t, J = 8.0 Hz, 1H), 4.05 (t, J = 5.3 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.39 (dd, J = 8.0 and 14.6 Hz, 1H), 3.34 (dd, J = 8.0 and 14.6 Hz, 1H), 3.16 (s, 3H), 3.14 (s, 3H), 3.06 (dd, J = 5.3 and 15.1 Hz, 1H), 2.85 (dd, J = 15.5 and 5.3 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR δ 149.03, 145.70, 145.60, 144.37, 143.79, 140.07, 137.29, 129.94 (CH × 2), 127.45 (CH × 2), 123.68 (CH), 123.53, 120.40 (CH), 114.22 (CH), 113.73, 111.89 (CH), 103.88 (CH), 100.61 (CH), 57.42 (CH_2), 56.61 (OMe), 56.29 (OMe), 54.93 (OMe × 2), 51.47 (CH_2), 39.24 (CH), 21.78 (Me). MS (FAB), *m*/*z* (%): 530 (M + 1, 1), 529 (2), 528 (2), 498 (3), 466 (3), 272 (9), 271 (9), 257 (100). Anal. Calcd for $C_{27}H_{31}NO_8S$, C 61.23, H 5.90, N 2.64. Found: C 61.24, H 5.90, N 2.32.

***N*-Tosyl-2,12b-dihydro-7-hydroxy-10,11-dimethoxy-1*H*-[1]benzopyrano[4,3,2-*ef*][3]benzazepine (14).** A mixture of acetal **13a** (1.219 g, 2.3 mmol), glacial acetic acid (50 mL), and 10% HCl (15 mL) under argon was heated at 75 °C for 0.5 h. The mixture was cooled, diluted with water, and extracted with CH_2Cl_2. The organic extract was washed with 5% K_2CO_3 solution and then with water, dried over anhydrous Na_2SO_4, and concentrated to a residue. This was column chromatographed (silica gel; 1% (v/v) EtOAC/hexane) to afford **14** (845 mg, 79%), which was recrystallized from EtOAc/*n*-hexane. Mp:152−153 °C. IR (NaCl) 3440 (OH), 1635, 1610, 1600, 1510, 1490, 1460, 1340, 1220, 1200, 1160, 1000, 920 cm^{-1}. ^1H NMR δ 7.75 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 6.83 (dd, J = 1.5 and 10.4 Hz, 1H), 6.78 (d, J = 1.5 Hz, 2H), 6.73 (s, 1H), 6.57 (s, 1H), 5.68 (d, J = 10.5 Hz, 1H), 5.53 (bs, 1H, OH), 4.58 (d, J = 13.6 Hz, 1H), 3.97 (d, J = 7.2 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.30 (dd, J = 13.6 and 7.2 Hz, 1H), 2.4 (s, 3H). ^{13}C NMR δ 149.53, 145.98, 144.55, 143.77, 142.82, 137.30, 136.09, 130.31 (CH × 2), 127.23 (CH × 2), 126.82, 124.75 (CH), 123.23 (CH), 121.29, 114.07 (CH), 110.89 (CH), 110.54, 109.58 (CH), 100.10 (CH), 57.07 (CH_2), 56.64 (OMe), 56.31 (OMe), 38.16 (CH), 21.82 (Me). MS *m*/*z* (%): 465 (M^+, 17), 311 (21), 310 (100), 294 (16), 282 (8), 265 (11), 221 (4), 155 (9). Anal. Calcd for $C_{25}H_{23}NO_6S$, C 64.50, H 4.98, N 3.01. Found: C 64.49, H 5.01, N 2.77.

***N*-Tosyl-2,3,4,12b-tetrahydro-7-hydroxy-10,11-dimethoxy-1*H*-[1]benzopyrano[4,3,2-*ef*][3]benzazepine (15).** Compound **14** (840 mg, 1.80 mmol) and 10% Pd/C (150 mg) in $CHCl_3$ (45 mL) were stirred under 1 atm of H_2 for 12 h. After filtration through Celite and evaporation of the $CHCl_3$ in vacuo, compound **15** (776 mg, 92%) was obtained and recrystallized from EtOAc/*n*-hexane. Mp: 207−208 °C. IR (NaCl) 3420 (OH), 1615, 1595, 1510, 1495, 1460, 1250, 1225, 1155, 1090, 1005, 730 cm^{-1}. ^1H NMR δ 7.63 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 6.90 (s, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.60 (s, 1H), 5.63 (s, 1H, OH), 4.40 (d, J = 8.6 Hz, 1H), 4.22 (d, J = 13.0 Hz, 1H), 4.20−4.17 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.21 (t, J = 12.6 Hz, 1H), 2.82 (dd, J = 5.7 and 15.1 Hz, 1H), 2.70 (dd, J = 8.6 and 13.0 Hz, 1H), 2.42 (t, J = 12.2 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR δ 149.38, 145.98, 143.91, 143.80, 143.08, 137.94, 135.60, 132.05, 130.02 (CH × 2), 127.32 (CH × 2), 123.67 (CH), 122.65, 113.55 (CH), 111.32, 111.24 (CH), 100.05 (CH), 58.11 (CH_2), 56.61 (OMe), 56.30 (OMe), 48.38 (CH_2), 38.98 (CH), 36.56 (CH_2), 21.74 (Me). MS *m*/*z* (%): 467 (M^+, 4), 313 (22), 312 (100), 285 (7), 271 (11), 270 (18), 226 (13). HRMS for $C_{25}H_{25}NO_6S$, 467.14026; found, 467.14039.

2,3,4,12b-Tetrahydro-7-hydroxy-10,11-dimethoxy-1*H*-[1]benzopyrano[4,3,2-*ef*][3]benzazepine (16). Tosylate **15** (560 mg, 1.19 mmol), 3% Na amalgam (29 g; Na equivalent, 37.8 mmol), and anhydrous Na_2HPO_4 (3.36 g, 23.7 mmol) were mixed under Ar in dry MeOH (200 mL) and then refluxed for 12 h. The cooled reaction mixture was filtered through Celite and concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 and water. The aqueous phase was separated and further extracted with CH_2Cl_2 (30 mL), and the combined organic extracts were washed with brine and then dried over anhydrous Na_2SO_4. The CH_2Cl_2 was removed in vacuo, and the residue was column chromatographed (silica gel; 8% (v/v) MeOH in CH_2Cl_2) to afford norclavizepine (**16**) (273 mg, 73%) as a foam which was crystallized from EtOAc/*n*-hexane. Mp: 211−213 °C dec. IR (KBr) 3440, 3240, 2930, 1505, 1450, 1250, 1225 cm^{-1}. ^1H NMR: δ 6.70−6.78 (m, 3H), 6.61 (s, 1H), 5.51 (bs, 1H), 4.30 (d, J = 9.5 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.36 (d, J = 13.0 Hz, 1H), 3.32−3.25 (m, 1H), 3.15−3.04 (m, 1H), 2.94 (dd, J = 13.0 and 9.5 Hz, 1H), 2.79−2.62 (m, 2H). ^{13}C NMR δ (DMSO-d_6): 148.76, 145.03, 143.77 (C × 2), 138.36,

132.31, 123.66, 122.94 (CH), 113.73 (CH), 112.25, 112.01 (CH), 100.24 (CH), 58.12 (CH_2), 56.08 (OMe), 55.76 (OMe), 47.53 (CH_2), 39.18 (CH), 37.12 (CH_2). MS *m*/*z* (%): 313 (M^+, 52), 284 (22), 283 (61), 271 (100), 257 (47), 239 (7), 226 (14). HRMS for $C_{18}H_{19}NO_4$, 313.13141; found, 313.13103.

***N*-Methyl-2,3,4,12b-tetrahydro-7-hydroxy-10,11-dimethoxy-1*H*-[1]benzopyrane[4,3,2-*ef*][3]benzazepine (1a).** Norclavizepine (**16**) (250 mg, 0.76 mmol), formic acid (2 mL), and 37% formaldehyde (2 mL) were mixed under argon and then heated at 80 °C for 3 h. The reaction mixture was cooled, water (5 mL) and 5% $NaHCO_3$ solution (10 mL) were added, and the resulting solution was extracted with CH_2Cl_2. The organic extract was washed with water, dried over anhydrous Na_2SO_4, and concentrated to a residue. Purification of this residue by column chromatography (silica gel; 5% (v/v) MeOH in CH_2Cl_2) allowed isolation of **1a** (235 mg, 90%), which was recrystallized from EtOAc/*n*-hexane. Mp: 214−216 °C dec. (234−235 °C for (−)-clavizepine,[1] 218−219 °C dec. for (±)-clavizepine[2a]). IR (KBr) 1610, 1515, 1460, 1440, 1415, 1250, 1230, 1205, 1175, 1125, 1030, 1005, 950, 870, 810 cm^{-1}. ^1H NMR: δ 6.85 (s, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 6.59 (s, 1H), 4.41 (d, J = 9.4 Hz, 1H), 3.87 (s, 6H), 3.23−3.11 (m, 3H), 2.71 (dd, J = 6.0 and 15.0 Hz, 1H), 2.46 (dd, J = 9.9 and 12.2 Hz, 1H), 2.45 (s, 3H), 2.15 (t, J = 11.8 Hz, 1H). ^{13}C NMR: δ 149.01, 145.72, 144.24, 142.87, 138.14, 133.40, 123.53, 122.92 (CH), 113.45 (CH), 113.11, 111.70 (CH), 100.08 (CH), 68.08 (CH_2), 57.52 (CH_2), 56.64 (OMe), 56.24 (OMe), 47.51 (NMe), 37.49 (CH), 35.36 (CH_2). MS *m*/*z* (%): 327 (M^+, 47), 312 (5), 284 (40), 283 (100), 271 (22), 270 (24), 269 (30), 226 (12). Anal. Calcd for $C_{19}H_{21}NO_4$: C 69.71, H 6.46, N 4.28. Found: C 69.62, H 6.63, N 4.03.

Acknowledgment. Financial support from the CICYT (SAF93-0607) is gratefully acknowledged. We also thank the Xunta de Galicia for a fellowship awarded to M.C.

Supporting Information Available: Spectroscopic and analytical data for 9-methylene-2,3-dimethoxy-5-(benzyloxy)-xanthene and 2,3-dimethoxy-5-(benzyloxy)xanthone, ^1H NMR spectrum of compound **5**, and ^1H and ^{13}C NMR spectra of compounds **6**, **7**, **8** (as a 2:1 mixture with an unknown compound), **9a**, **9c**, **10**, **11**, **12**, **13a**, **13c**, **14**, **15**, **16**, and **1a** (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960291N