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Total Synthesis of (±)-*O*-Methylclavizepine

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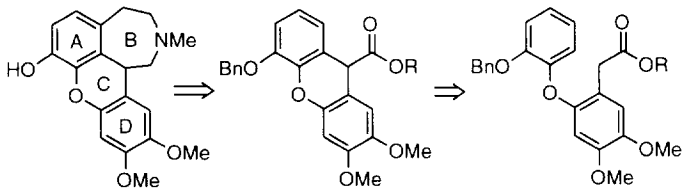
Abstract. The total synthesis of *O*-methylclavizepine (**3b**) from dibenzoxepinone **4** is described. Overall yield was 21% in nine steps.

(-)-Clavizepine (**3a**) is the only known alkaloid with a dibenzopyranazepine skeleton.[1] Its precise biogenesis is not known, but it might be derived from the cularines[2] via contraction of the oxepine ring and concomitant expansion of the nitrogen-containing ring.

Recently, Ikeda's[3] group and our own[4] have reported alternative total syntheses of clavizepine based on the retrosynthetic analysis shown in Scheme 1, which features xanthene-9-carboxylate **2** as the key intermediate.

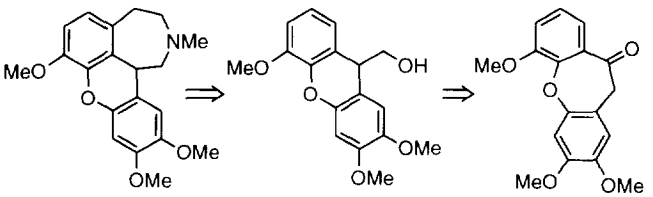


3a **2** **1**

Scheme 1

Ikeda's group prepared **2** in 65% yield by cyclization of an α-keto ester, and formed the azepine ring by Pummerer rearrangement of a sulfoxide (95% yield). The overall yield for their 16 step synthesis was 7.9% from 4-bromoveratrole. Our shorter synthesis afforded clavizepine in 12 steps and in 3.7% overall yield from 3,4-dimethoxyphenylacetic acid, and involved intramolecular addition of an ester enolate to a benzyne for preparation of **2** (60% yield), and aromatic substitution by an amido acetal for formation of the azepine ring (58% yield).

In this paper, we described an alternative, more efficient, approach to dibenzopyranazepines that is based on the retrosynthetic analysis shown in Scheme 2. The key step of this synthesis is contraction of the oxepine ring of dibenzoxepinone **4** to give the dibenzopyran **5**, from which the nitrogenated ring can be assembled to afford *O*-methylclavizepine (**3b**).[1]

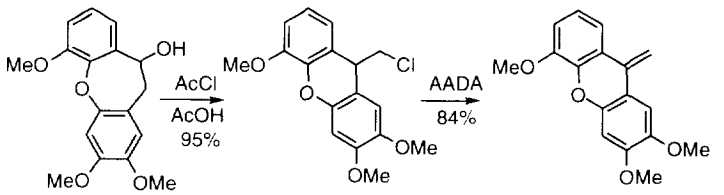


3b **5** **4**

Scheme 2

We have previously used dibenzoxepinones in the synthesis of several different cularine alkaloids,[5] but to our knowledge they have never been used in the synthesis of clavizepine derivatives, which thus represents an extension of their synthetic utility.

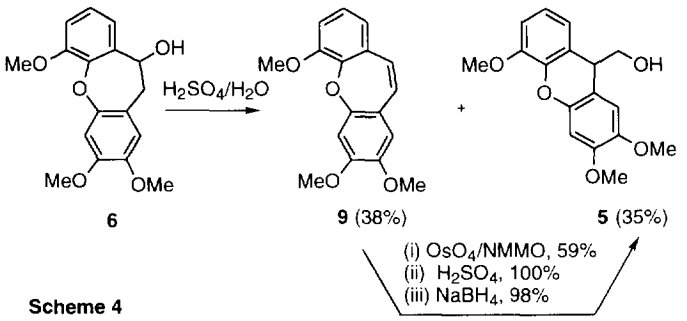
Firstly, the starting dibenzoxepinone **4**[6] was reduced to dibenzoxepinol (**6**). Contraction of this ring system has been studied by Kametani and co-workers, who have described the transformation of **6** into 9-chloromethylxanthene (**7**).[7] However, repeated attempts to aminate this chloride gave the elimination product **8** preferentially. Thus, treatment of **7** with aminoacetaldehyde dimethyl acetal (excess or in the presence of K_2CO_3) in DMF gave **8** in 84% yield (Scheme 3); reaction of **7** with the anion of *N*-tosylaminoacetaldehyde (generated by addition of one equivalent of NaH in DMF) gave **8** in 80% yield; and treatment of a solution of **7** in DMF with NaN_3 at 70°C afforded a 70% yield of **8** and only a 15% yield of the substitution product.



6 **7** **8**

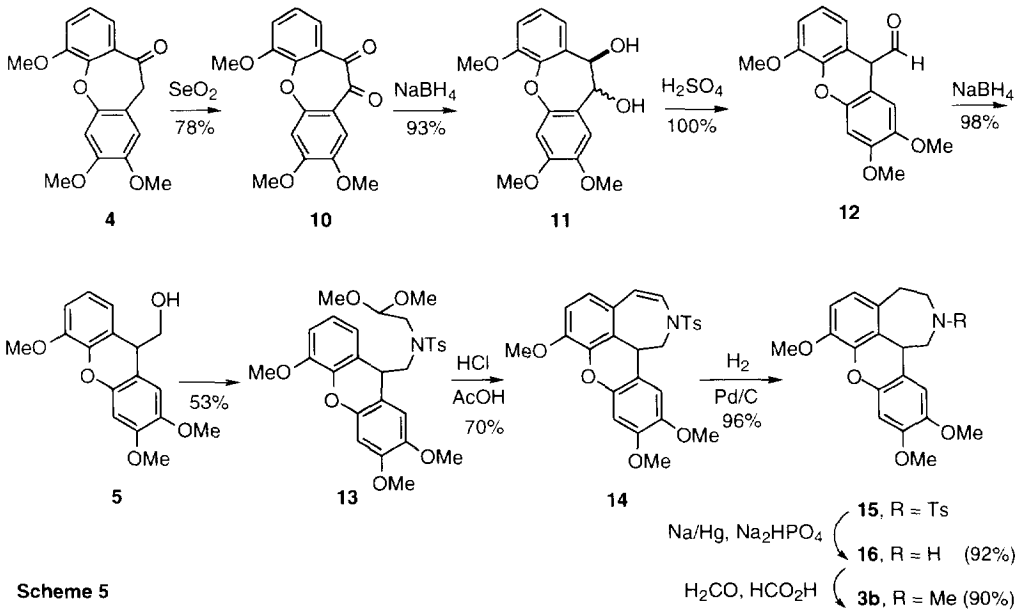
Scheme 3

In the light of these results, we switched our attention to hydroxymethyl derivative **5**, which is susceptible of amination by *N*-tosylaminoacetaldehyde under conditions recently described by our group.[8] Treatment of a solution of alcohol **6** in aqueous dioxane with H_2SO_4 at 110°C afforded a 38% yield of elimination product **9**, a 35% yield of the rearranged alcohol **5**, and a 15% yield of unchanged starting alcohol **6**. The undesired elimination product **9** could be converted to alcohol **5** by (i) *syn*-hydroxylation of the double bond using OsO_4/NMMO; (ii) pinacol rearrangement to xanthen-9-carboxaldehyde (**12**) ; and (iii) reduction of this (57% overall yield).



Scheme 4

This difficult and rather low-yielding approach to **5** was unsatisfactory, and so we developed an alternative synthesis of **5** that began with SeO_2 oxidation of ketone **4** to α-diketone **10**. Reduction of **10** then gave a mixture of *cis* and *trans* diols **11** that could be converted to **5** in almost quantitative yield by pinacol rearrangement and subsequent reduction (71% overall yield from **4**).



Scheme 5

Mitsunobu reaction of alcohol **5** with *N*-tosyl aminoacetaldehyde dimethyl acetal gave dimethylacetal **13**, which cyclized under acidic conditions to **14**. Finally, catalytic hydrogenation of **14** gave the *N*-tosylated compound **15**, which, following reductive cleavage of the sulfonamide and *N*-methylation of amine **16**, gave (±)-*O*-methylclavizepine **3b.**

In summary, the first total synthesis of (±)-*O*-methylclavizepine (**3b**) was accomplished in only nine steps and 21% overall yield from dibenzoxepinone **4**. The synthesis of (±)-clavizepine (**3a**) by this approach is under way.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 250.13 and 62.83 MHz respectively, using TMS as internal reference. MS were recorded at an ionization voltage of 70 eV. Melting points are uncorrected. Reagents and solvents were purified and dried using standard methods.

10,11-dihydro-2,3,6-trimethoxydibenz[*b,f*]oxepin-10-ol (6): To dibenzoxepinone **4**[6] (1 g, 3.3 mmol) dissolved in methanol (50 mL), $NaBH_4$ (excess) was carefully added in small portions until no starting oxepinone 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, after recrystallization from MeOH, 0.95 g of alcohol **6** (98% yield). m.p.: 168-169°C (Lit.[7] 169-170°C). IR (KBr), ν: 3525 (OH), 1625, 1515, 1480, 1270, 1200, 1100, 1045, 995 cm^{-1}. ^{1}H NMR, δ: 7.11-7.00 (m, 2H), 6.88-6.84 (m, 2H), 6.66 (s, 1H), 5.21-5.19 (m, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.44 (dd, J = 14.8 and 3.4 Hz, 1H), 3.10 (dd, J = 14.8 and 8.0 Hz, 1H), 2.18 (d, J = 7.8 Hz, 1H, OH). ^{13}C NMR, δ: 151.43, 150.99, 148.34, 146.13, 145.61, 135.55, 124.65 (CH), 120.86 (CH), 119.61, 113.69 (CH), 111.69 (CH), 105.85 (CH), 69.41 (CH), 56.67 (OCH_3), 56.60 (OCH_3), 56.52 (OCH_3), 38.92 (CH_2). MS m/z (%): 302 (M^+, 100), 271 (21), 227 (5), 151 (19), 137 (12).

Ring contraction of dibenzoxepinol 6: To a solution of alcohol **6** (1 g, 3.31 mmol) in dioxane (10 mL), 10 mL of aqueous H_2SO_4 (4%) were added. The mixture was heated at 110°C under Ar for 12 h, and then concentrated in a rotary evaporator. The residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was separated and further extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4 and concentrated to a residue, which was column chromatographed (silica gel; 1:1 EtOAc/*n*-hexane). In order of elution, 415 mg (38%) of **9**, 160 mg (16%) of the starting material and 345 mg (35%) of **5** were isolated.

9-Hydroxymethyl-2,3,5-trimethoxy-9H-xanthene (**5**): Recrystallized from EtOAc/*n*-hexane, m.p.:148-150 °C. IR (KBr), ν: 3540 (OH), 1615, 1580, 1490, 1270, 1220, 1120, 1090 cm^{-1}. ^{1}H NMR, δ: 7.03 (t, J = 7.8 Hz, 1H), 6.89-6.83 (m, 3H), 6.74 (s, 1H), 4.03 (t, J = 5.7 Hz, 1H), 3.94 (s, 3H), 3.87 (s, 6H), 3.72 (d, J = 5.7 Hz, 2H). ^{13}C NMR, δ: 149.01, 147.92, 146.04, 145.33, 141.91, 122.71 (CH), 120.68 (CH), 112.34, 111.31 (CH), 110.43 (CH),101.07 (CH), 68.99 (CH_2), 56.40 (OCH_3), 55.99 (OCH_3 x 2), 41.69 (CH). MS m/z (%): 302 (M^+, 3), 271 (100), 227 (7), 185 (2), 155 (2), 139 (2), 69 (4). Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54, H, 6.00; Found: C, 67.65, H, 5.92.

2,3,6-Trimethoxydibenz[b,f]oxepine (**9**): Recrystallized from EtOAc/*n*-hexane, m.p.: 90-91°C. IR (KBr), ν: 1600, 1500, 1465, 1435, 1260, 1200, 1180, 1160, 1105, 995, 860 cm^{-1}. ^{1}H NMR, δ: 7.04 (t, J = 7.9 Hz, 1H), 6.92 (m, 2H), 6.74 (dd, J = 7.6 and 1.5 Hz, 1H), , 6.67 (s, 2H), 6.64 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H). ^{13}C NMR, δ: 151.51, 150.91, 150.28, 145.91, 145.18, 131.83, 129.74 (CH), 128.26 (CH), 124.46 (CH), 122.35, 120.50 (CH), 112.11 (CH), 110.99 (CH), 105.71 (CH), 56.00 (OCH_3), 55.90 (OCH_3). MS m/z (%): 284 (M^+,100), 269 (14), 241 (11), 226 (5). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82, H, 5.67; Found: C, 71.71, H, 5.70.

***cis*-10,11-Dihydro-2,3,6-trimethoxydibenz[b,f]oxepin-10,11-diol (11)** To compound **9** (0.4 g, 1.4 mmol) dissolved in THF (4 mL) were added *N*-methylmorpholine-*N*-oxide monohydrate (200 mg, 1.48 mmol) and 2 mL of a $5.6x10^{-3}$M solution of OsO_4 (0.011 mmol). The mixture was stirred overnight at r.t., and poured into an ice cooled mixture of 10% HCl and 15% sodium bisulfite (5:1 v/v). This solution was extracted with EtOAc, which was then 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 *cis*-diol **11** (256 mg, 59%), m.p.:165-167 °C. IR (KBr), ν: 3280 (OH), 3375 (OH), 1610, 1510, 1480, 1450, 1260, 1210, 115, 1045, 860 cm^{-1}. ^1H NMR, δ ($CDCl_3$): 7.06-7.03 (m, 2H), 6.83 (s, 1H), 6.81-6.79 (m, 1H), 6.78 (s, 1H), 5.28 (s, 1H), 4.97 (s, 1H), 3.82 (s, 6H), 3.78 (s, 3H). δ (DMSO-d_6): 7.07-7.03 (m, 2H), 6.93 (m, 2H), 6.68 (s, 1H), 5.45 (d, J = 5.7 Hz, 1H, OH), 5.21 (d, J = 5.2 Hz, 1H, OH), 5.13 (dd, J = 5.7 and 1.9 Hz, 1H), 4.88 (dd, J = 5.2 and 1.9 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.70 (s, 3H). ^{13}C NMR, d (DMSO-d_6):150.51, 148.46, 148.10, 145.13, 143.56, 134.99, 123.93 (CH), 122.58, 120.47 (CH), 114.39 (CH), 111.21 (CH), 104.74 (CH), 71.92 (CH), 70.59 (CH), 56.20 (OCH_3), 56.03 (OCH_3), 55.83 (OCH_3). MS m/z (%): 318 (M^+, 36), 300 (30), 271 (100), 227 (8), 167 (13), 139 (8). HRMS Calcd for $C_{17}H_{18}O_6$, 318.11034; found, 318.11061.

2,3,5-Trimethoxy-9*H*-xanthene-9-carboxaldehyde (12): *Cis*-diol **11** (288 mg, 0.91 mmol) was dissolved in glacial acetic acid (2 mL) , which was then de-aerated by bubbling argon through it, and a drop of conc.H_2SO_4 was added. The mixture was stirred for 3 min at r.t., 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, and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Aldehyde **12** (271 mg, 100%) was obtained as a foam that would not crystallize. IR (NaCl), ν: 1720 (CO), 1610, 1580, 1510, 1485, 1410, 1275, 1220, 1120, 1090, 1015, 730 cm^{-1}. ^1H NMR. δ: 9.27 (d, J = 3.7 Hz, 1H), 6.82 (t, J = 7.6 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.59 (s, 1H), 6.55 (d, J = 7.6 Hz, 1H), 6.40 (s, 1H), 4.45 (d, J = 3.7 Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H). ^{13}C NMR, δ: 195.57 (CO), 150.07, 148.43, 145.72, 144.99, 140.90, 123.21 (CH), 121.02 (CH), 115.81, 111.57 (CH), 110.81 (CH), 105.23, 101.29 (CH), 56.32 (OCH_3), 56.07 (OCH_3), 55.05 (OCH_3), 51.83 (CH). MS (FAB), m/z: 302 (M+2, 1), 301 (M+1, 17), 300 (M^+, 9), 299 (23), 287 (22), 272 (40), 271 (100), 257 (15).

9-Hydroxymethyl-2,3,5-trimethoxy-9H-xanthene (5): Reduction of aldehyde **12** (282 mg, 0.94 mmol) with $NaBH_4$, as described for preparation of **6**, gave alcohol **5** (278 mg, 98%).

2,3,5-Trimethoxydibenz[*b,f*]oxepin-10,11-dione (10): Ketone **4**[6] (0.545 mg, 1.8 mmol), SeO_2 (0.403 mg, 3.6 mmol), glacial acetic acid (5 mL) and water (2 mL) were mixed and then heated at 90°C under argon for 12 h. After cooling the reaction mixture, it was 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, and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography of the residue (silica gel; CH_2Cl_2) afforded diketone **10** (0.445 g, 78%), which was recrystallized from EtOAc/*n*-hexane to afford an intensely yellow crystalline solid, m.p.:147- 149 °C. IR (NaCl), ν: 1660, 1605, 1510, 1440, 1410,1270, 1230, 1090, 1000 cm^{-1}. ^1H NMR, δ: 7.48 (s, 1H), 7.38 (dd, J = 7.9 and 1.6 Hz, 1H), 7.24 (t, J = 7.9 Hz, 1H), 7.17 (dd, J = 7.9 and 1.6 Hz, 1H), 6.95 (s, 1H), 4.02 (s, 3H), 3.98 (s, 3H), 3.93 (s, 3H). ^{13}C NMR, δ: 188.57 (CO), 183.71 (CO), 156.29, 154.96, 151.42, 147.21, 146.35, 129.51, 126.26 (CH), 122.22 (CH), 118.22, 117.05 (CH),

111.16 (CH), 104.75 (CH), 57.10 (OCH_3), 56.88 (OCH_3), 56.74 (OCH_3). MS m/z (%): 314 (M^+, 39), 283 (100), 271 (10), 243 (19), 228 (15), 200 (14), 129 (5). Anal. Calcd for $C_{17}H_{14}O_6$: C, 64.97, H, 4.49; Found: C, 64.87, H, 4.56.

Reduction of diketone (10): Diketone **10** (100 mg, 0.318 mmol) was dissolved in MeOH (5 mL), and a small excess of $NaBH_4$ was added. The mixture was stirred for a few minutes, and then neutralized by dropwise addition of 5% HCl and diluted with water. This solution was extracted with CH_2Cl_2, and the organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. ^1H NMR of the residue indicated that it was a 1:1 mixture of the *cis* and *trans* -diols **11** (94 mg, 93%).

trans-10, 11-Dihydro-2,3,6-trimethoxydibenz[b,f]oxepin-10,11-diol (**11**): Preparative tlc (silica gel), developing the plate several times using 3% (v/v) MeOH in CH_2Cl_2, allowed the separation of the slower moving compound, obtained as crystalline solid, m.p.:156-158°C. IR (KBr), ν: 3350 (OH), 3200 (OH), 1610, 1505, 1405, 1250, 1200, 1180, 900, 850, 750 cm^{-1}. ^1H NMR, δ: 7.18 (dd, J = 7.9 and 1.5 Hz, 1H), 7.10 (t, J = 7.9 Hz, 1H), 6.99 (s, 1H), 6.84 (dd, J = 7.9 and 1.5 Hz, 1H), 6.81 (s, 1H), 5.19 (d, J = 9.2 Hz, 1H), 4.72 (d, J = 9.2 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.06 (s broad, 1H, OH), 2.81 (s broad, 1H, OH). ^{13}C NMR, δ: 150.92, 149.60, 149.05, 146.02, 145.69, 133.19, 125.01 (CH), 121.08, 118.56 (CH), 111.86 (CH), 111.50 (CH), 105.02 (CH), 73.37 (CH), 72.77 (CH), 56.24 (OCH_3), 56.10 (OCH_3 x 2). MS m/z (%): 318 (M^+, 27), 301 (9), 300 (28), 271 (100), 269 (59), 256 (12). HRMS Calcd for $C_{17}H_{18}O_6$, 318.11034; found, 318.10992.

***N*-(2,2-Dimethoxyethyl), *N*-tosyl-9-aminomethyl-2,3,5-trimethoxy-9H-xanthene (13):** Alcohol **5** (1 g, 3.31 mmol), *N*-tosyl aminoacetaldehyde dimethyl acetal and triphenylphosphine (2.7 g, 10 mmol) were dissolved in dry THF (37 mL) under argon. Diethyl azodicarboxylate (1.4 mL, 8.9 mmol) was added, and the mixture was stirred for 3 h at r.t. 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 afford **13** (0.95 g, 53%) as a foam. IR (NaCl), ν: 1610, 1580, 1510, 1490-1440, 1340, 1270, 1220, 1160, 1120, 1090, 1010, 970, 860, 820, 790 cm^{-1}. ^1H NMR, δ: 7.69 (d, J = 8.1Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 7.00 (t, J = 7.8 Hz, 1H), 6.87-6.81 (m, 2H), 6.79 (s, 1H), 6.77 (s, 1H), 4.35 (m, 1H), 4.01 (m, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.43 (dd, J = 14.6 and 6.5, 1H), 3.30 (dd, J = 14.6 and 8.5, 1H), 3.11 (s, 3H), 3.10 (s, 3H), 3.00 (dd, J = 15.6 and 5.3 Hz, 1H), 2.87 (dd, J = 15.6 and 5.6 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR, δ: 148.66, 147.67, 145.64, 145.05, 143.13, 141.62, 136.91, 129.34 (CH x 2), 126.90 (CH x 2), 123.36, 122.63 (CH), 120.58 (CH), 112.98, 111.34 (CH), 110.24 (CH), 103.12 (CH), 100.61 (CH), 56.75 (CH_2), 56.00 (OCH_3), 55.71 (OCH_3), 55.65 (OCH_3), 53.95 (OCH_3 x 2), 50.71 (CH_2), 38.75 (CH), 21.00 (CH_3). MS (FAB), m/z (%): 544 (M+1, 1), 543 (M^+, 5), 542 (3), 512 (6), 480 (11), 272 (32), 271 (100).

***N*-Tosyl-2,12b-dihydro-7,10,11-trimethoxy-1*H*-[1]benzopyrane[4,3,2-*ef*][3]benz-azepine(14):** A mixture of acetal **13** (652 mg, 1.2 mmol), glacial acetic acid (24 mL) and 10% HCl (6 mL) under argon was heated at 75°C for 2 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, and dried over

anhydrous Na_2SO_4 and concentrated to a residue. This was column chromatographed (silica gel; 1% (v/v) MeOH in CH_2Cl_2) to afford **14** (400 mg, 70%), which was recrystallized from EtOAc/*n*-hexane, m.p.:201-202°C. IR (KBr), ν: 1635, 1515, 1490, 1435, 1410, 1345, 1270, 1225, 1165, 1095, 1025, 810 cm^{-1}. ^1H NMR, δ: 7.75 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 6.88-6.74 (m, 3 H), 6.69 (s, 1H), 6.67 (s, 1H), 5.68 (d, J = 10.5 Hz, 1H), 4.55 (d, J = 13.7 Hz, 1H), 4.01 (d, J = 7.0 Hz, 1H), 3.90 (s, 6H), 3.85 (s, 3H), 3.31 (dd, J = 13.7 and 7.0 Hz, 1H), 2.4 (s, 3H). ^{13}C NMR, δ: 149.22, 146.18, 145.46, 144.09, 143.98, 138.95, 135.90, 129.90 (CH x 2), 127.11, 126.86 (CH x 2), 123.75 (CH), 123.11 (CH), 121.37, 110.51, 110.09 (CH), 109.93 (CH), 108.96 (CH), 100.22 (CH), 57.10 (CH_2), 56.21 (OCH_3), 55.92 (OCH_3), 55.82 (OCH_3), 37.80 (CH), 21.25 (CH_3). MS m/z (%): 479 (M^+, 14) 325 (22), 324 (100), 308 (9), 281 (8), 265 (4), 154 (4). Anal. Calcd for $C_{26}H_{25}NO_6S$, C 65.12, H 5.25, N, 2.92; found, C 64.98, H 5.26, N, 2.61.

***N*-Tosyl-2,3,4,12b-tetrahydro-7,10,11-trimethoxy-1*H*-[1]benzopyrane [4,3,2-ef][3] benzazepine (15)**: Compound **14** (126 mg, 0.263mmol) and 10% Pd/C (20 mg) in $CHCl_3$ (20 mL) were stirred under 1 atm. of H_2 for 12 h. After filtration through Celite and evaporation of the $CHCl_3$ *in vacuo*, tosylate **15** (122 mg, 96%) was obtained and recrystallized from EtOAc/n-hexane, m.p.:201-202 °C. IR (KBr), ν: 1500, 1440, 1410, 1335, 1280, 1265, 1255, 1230, 1210, 1160, 1120, 1090, 850, 730 cm^{-1}. ^1H NMR, δ: 7.62 (d, J = 7.7 Hz, 2H), 7.25 (s, J = 7.7 Hz, 2H), 6.88 (s, 1H), 6.76 (d, J = 7.6 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.70 (s, 1H), 4.44 (d, J = 9.1 Hz, 1H), 4.26-4.18 (m, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.22 (m, 1H), 2.85 (dd, J = 15.1 and 5.7 Hz, 1H), 2.70 (dd, J = 13.3 and 9.1 Hz, 1H), 2.42 (m, 1H), 2.37 (s, 3H). ^{13}C NMR, δ: 149.21, 146.59, 145.62, 144.16, 143.37, 139.72, 135.65, 132.48, 129.67 (CH x 2), 127.04 (CH x 2), 122.87, 122.79 (CH), 110.94, 110.82 (CH), 109.72 (CH), 100.28 (CH), 58.00 (CH_2), 56.26 (OCH_3), 55.96 (OCH_3), 47.97 (CH_2), 38.71 (CH), 36.26 (CH_2), 21.26 (CH_3). MS m/z (%): 481 (M^+, 3), 382 (1), 327 (23),326 (100), 285 (5), 269 (26). HRMS Calcd for $C_{26}H_{27}NO_6S$, 481.15591; found, 481.15587.

2,3,4,12b-Tetrahydro-7,10,11-trimethoxy-1*H*-[1]benzopyrane [4,3,2-ef][3]benzazepine (16): Tosylate **15** (105 mg, 0.218 mmol), 3% Na amalgam (4.5 g; Na equivalent, 5.8 mmol) and anhydrous Na_2HPO_4 (157 mg, 1.1 mmol) were mixed under Ar in dry MeOH (35 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 amine **16** (66 mg, 92%) as a foam. IR (NaCl), ν: 3017, 1613, 1585, 1502, 1379, 1261, 1126, 1096 cm^{-1}. MS m/z (%): 327 (M^+, 59), 297 (53), 285 (100), 271 (59), 225 (10). ^1H NMR, δ: 6.77-6.67 (m, 4H), 4.28 (d, J = 8.9 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 6H), 3.33-3.21 (m, 2H), 3.07 (m, 1H), 2.91 (dd, J = 13.1 and 8.9 Hz, 1H), 2.73 (dd, J = 14.7 and 4.3 Hz, 1H), 2.64 (m, 1H), 2.23 (s broad, 1H, NH). ^{13}C NMR, δ: 148.94, 146.52, 145.43, 144.34, 139.97, 134.25, 123.96, 122.72 (CH), 112.55, 111.21 (CH), 109.65 (CH), 100.62 (CH), 59.18 (CH_2), 56.60 (OCH_3), 56.35 (OCH_3), 56.27 (OCH_3), 48.27 (CH_2), 40.87 (CH) 38.54 (CH_2). HRMS Calcd for $C_{19}H_{21}NO_4$, 327.14706; found, 327. 14733.

(±)-*O*-Methylclavizepine (3b): Amine **16** (61 mg, 0.18 mmol), formic acid (1 mL) and formaldehyde (1 mL) were mixed under argon and then heated at 80°C for 3 h. The reaction mixture was cooled, water (5 mL) and 15% NaOH solution (5 mL) were added, and the solution resulting was extracted with CH_2Cl_2 . The organic extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated to a residue. Preparative tlc (silica gel; 5% (v/v) MeOH in CH_2Cl_2) of this residue allowed isolation of **3b** (57 mg, 90%), which was recrystallized from EtOAc/*n*-hexane, m.p.:160-162 °C. IR (NaCl), ν: 1610, 1580, 1500, 1465, 1440, 1265, 1220, 1210, 115, 1090, 1000, 800 cm^{-1}. ^1H NMR, δ: 6.76-6.67 (m, 4H), 4.36 (d, J = 9.5 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 6H), 3.13-3.05 (m, 3H), 2.69 (dd, J = 14.8 and 6.1 Hz, 1H), 2.42 (dd, J = 12.4 and 9.5 Hz, 1H), 2.38 (s, 3H), 2.07 (m, 1H). ^{13}C NMR, δ: 148.96, 146.46, 145.53, 144.63, 139.85, 134.16, 123.98, 122.33 (CH), 112.79, 111.36 (CH), 109.69 (CH), 100.58 (CH), 68.42 (CH_2), 57.57 (CH_2), 56.62 (OCH_3), 56.35 (OCH_3), 56.28 (OCH_3), 47.52 (NMe), 37.67 (CH), 35.52 (CH_2). MS m/z (%): 341 (M^+, 43), 298 (36), 297 (100), 285 (36), 283 (44), 269 (30), 225 (7), 149 (5). MS m/z (%): 341 (M^+, 43), 298 (36), 297 (100), 285 (36), 283 (44), 269 (30), 225 (7), 149 (5). HRMS Calcd for $C_{20}H_{23}NO_4$, 341.16271; found, 341.16293.

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