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Synthesis and Receptor Binding Evaluation of Clavizepine Analogues with No Ring D Substituents†

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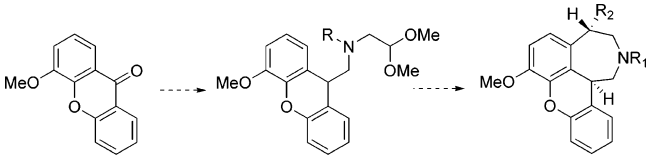

Assembly of the azepine ring of xantheno[9,1-*cd*]azepines by electrophilic cyclization of sulfonamide acetals provides access to clavizepine analogues in the form of 2,12b-dihydro- or 4-hydroxy-2,3,4,12b-tetrahydro-1*H*-xantheno[9,1-*cd*]azepines, in the latter case producing the trans derivative stereoselectively. Binding assays for clavizepine and analogues at adrenergic, dopaminergic, and serotonergic receptors are reported.

(−)-Clavizepine (**1a**) is a natural product that was first isolated from *Corydalis claviculata* (L.) DC in 1986[1] and was soon afterward found in *Sarcocapnos crassifolia* subsp. *speciosa*,[2] both of which are plants belonging to the Fumariaceae family. There have been no further reports of the isolation of this compound, which to date is the only known alkaloid incorporating a chromeno-3-benzazepine structure. In the mid 1990s, the total synthesis of racemic clavizepine was achieved by Ikeda's[3] group and our own,[4] and both approaches featured a xanthene-9-carboxylate as the key intermediate. Shortly afterward, we reported alternative syntheses of racemic clavizepine[5] and its *O*-methyl analogue **1b**[6] that featured a 9-hydroxymethylxanthene as the key intermediate. Synthetic samples of *rac*-clavizepine **1a**, its *O*-methyl analogue **1b**, and a few of their synthetic precursors have shown promising biological activities, as they exhibit affinity for several receptors (vide infra). This has encouraged us to synthesize some new analogues, such as D-ring-unsubstituted derivatives **10** and **13** for structure−activity studies. To this end, we selected as the key intermediate the 9-hydroxymethylxanthene derivative **5** (Scheme 1), which the annulation techniques developed by us in the earlier syntheses were expected to convert into the final target.

The required hydroxymethylxanthene **5** was prepared on a large scale in 67% overall yield by anti-Markovnikov hydration of methylenexanthene **4**, which was prepared from xanthone **2**[7] by addition of methylmagnesium chloride followed by dehydration of the resulting tertiary alcohol **3** (Scheme 2).

Unfortunately, reaction of **5** with *N*-tosyl aminoacetaldehyde dimethyl acetal under standard Mitsunobu conditions[8] afforded only a disappointing 30% yield of the desired nitrogenated product **6a** (Scheme 3), the main product being the methylene derivative **4** (64%). That the yield was lower than the 53% achieved in the corresponding reaction with the trimethoxy-substituted analogue of **5** during synthesis of **1b**[6] indicates that the dimethoxylated ring somehow favors the intermediate alkoxyphosphonium salt undergoing substitution rather than elimination.[9] In other cases in which phenethyl alcohols have undergone elimination, even when the more reactive (Boc)NHTs or (Cbz)NHTs have been used,[10] dehydration has been prevented by addition of pyridine[11] (although other authors have simply avoided the Mitsunobu reaction, aminating by indirect routes).[12] In this work, we tackled the problem by using one of the alternative kinds of sulfonamide that has been put forward as potentially more efficient than *N*-tosyl derivatives,[13,14] namely an *N*-trifluoromethanesulfonamide; and in the event, *N*-(dimethoxyethyl)-trifluoromethanesulfonamide did indeed prove to be very efficient for amination of hydroxymethylxanthene **5**, affording the triflamide **6b** in 80% yield after chromatographic removal of very minor amounts of the elimination product.

The dimethyl acetals **6a** and **6b** were cyclized under acidic conditions (HCl, AcOH, 75−80 °C) to **7a** (87%) and **7b** (84%), which by catalytic hydrogenation afforded the azepines **8a** (100%) and **8b** (90%) (Scheme 3). Reductive cleavage of the sulfonamide[15] and the triflamide[16] gave amine **9** in good yield

† Dedicated to Prof. R. Suau on the occasion of his 60th birthday.

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(1) Boente, J. M.; Castedo, L.; Domínguez, D.; Ferro, M. C. *Tetrahedron Lett.* **1986**, *27*, 4077−4078.

(2) Castedo, L.; López S.; Rodríguez de Lera, A.; Villaverde, M. C. *Phytochemistry* **1988**, *28*, 251−257.

(3) (a) Ishibashi, H.; Takagaki, K.; Imada, N.; Ikeda, M. *Synlett* **1994**, 49−50. (b) Ishibashi, H.; Takagaki, K.; Imada, N.; Ikeda, M. *Tetrahedron* **1994**, *50*, 10215−10224.

(4) Vázquez, R.; de la Fuente, M. C.; Castedo, L.; Domínguez, D. *Synlett* **1994**, 433−434.

(5) de la Fuente, M. C.; Castedo, L.; Domínguez, D. *J. Org. Chem.* **1996**, *61*, 5818−5822.

(6) de la Fuente, M. C.; Castedo, L.; Domínguez, D. *Tetrahedron* **1996**, *52*, 4917−4924.

(7) Galt, R. H. B.; Horbury, J.; Matusiack, Z. S.; Pearce, R. J.; Shaw, J. S. *J. Med. Chem.* **1989**, *32*, 2357−2362.

(8) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335−656.

(9) This effect of para- and ortho-substituted aryl rings has been invoked to explain the observed racemization of homochiral benzylic alcohols during the Mitsunobu reaction: (a) Iida, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1985**, *26*, 3255−3258. (b) Brown, R. F. C.; Jackson, W. R.; McCarthy, T. D. *Tetrahedron* **1994**, *50*, 5469−5488. (c) Kaufman, T. *Tetrahedron Lett.* **1996**, *37*, 5329−5332.

(10) Zhai, H.; Luo, Sh.; Ye, Ch.; Ma, Y. *J. Org. Chem.* **2003**, *68*, 8268−8271.

(11) Wovkulich, P. M.; Shankaran, K.; Kiegiel, J.; Uskokovic, M. R. *J. Org. Chem.* **1993**, *58*, 832−839.

(12) Feldman, K. S.; Cutarelli, T. D.; Di Florio, R. *J. Org. Chem.* **2002**, *67*, 8528−8537.

(13) Fukuyama, T.; Cheung, M.; Kan, T. *Synlett* **1999**, 1301−1303.

(14) Edwards, M. L.; Stemerick, D. M.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 3417−3420.

(15) Birkinshaw, T. N.; Holmes, A. B. *Tetrahedron Lett.* **1987**, *28*, 813−816.

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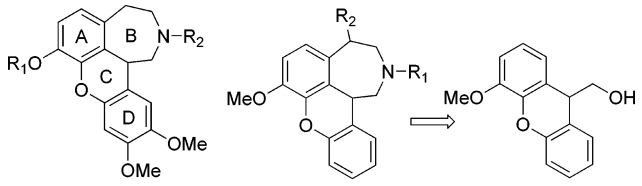
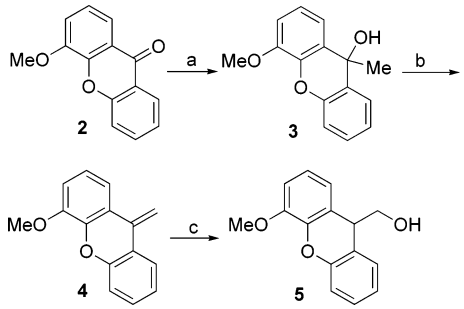
SCHEME 1



1a, R_1= H, R_2= Me
1b, R_1= Me, R_2= Me
1c, R_1= H, R_2= H
1d, R_1= H, R_2= Ts

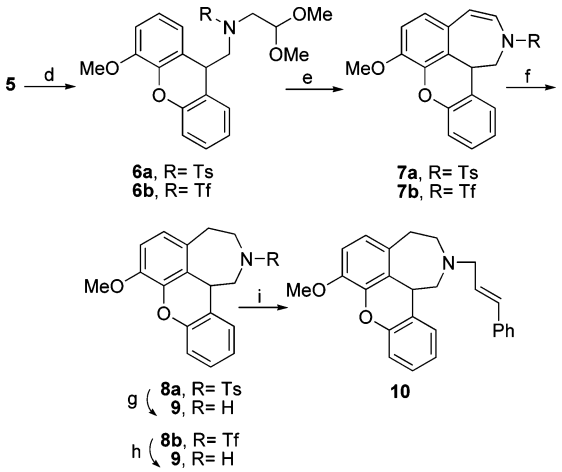
10, R_1= CH_2CH=CHPh, R_2= H
13, R_1= Ts, R_2= OH

SCHEME 2[a]



[a] Reagents and conditions: (a) MeMgCl (1.2 equiv), THF, 0 °C to room temperature (rt), 1 h; (b) EtOAc, AcOH, rt, 5 min; (c) (i) BH_3-SMe_2 (1.2 equiv), THF, 0 °C to rt, 1 h; (ii) H_2O_2/NaOH, rt, 1 h, 67% overall yield.

SCHEME 3[a]

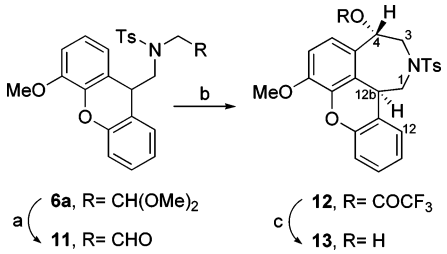


[a] Reagents and conditions: (d) For **6a**: *N*-tosyl aminoacetaldehyde dimethyl acetal, Ph_3P, DEAD, THF, rt, 3 h, 30%; for **6b**: *N*-trifluoromethanesulfonyl aminoacetaldehyde dimethyl acetal, Ph_3P, DEAD, THF, rt, 5 h, 80%; (e) HCl, AcOH, 80 °C, 87% for **7a**, 84% for **7b**; (f) H_2 (1 atm), 10% Pd/C, THF, rt, 12 h, 100% for **8a**, 90% for **8b**; (g) Na/Hg, Na_2HPO_4, MeOH, reflux, 12 h, 95%; (h) Red-Al, toluene, reflux, 85%; (i) cinnamaldehyde, MeOH; (ii) $NaCNBH_3$, 50%.

in both cases. The final cinnamyl derivative **10** was obtained by reductive amination of *trans*-cinnamaldehyde with amine **9**.

We also prepared the hydroxy derivative **13**, for which purpose the sulfonamido aldehyde **11** was obtained by mild hydrolysis of acetal **6a** at room temperature (Scheme 4). TFA cyclization of **11** afforded the trifluoroacetylated compound **12**, hydrolysis of which gave the desired product, **13**. The suspicion that in the cyclization reaction the initial formation of **13** had been followed by esterification to **12** was supported when the proton NMR spectrum of a sample of **13** subjected to the cyclization conditions showed the exclusive formation of trifluoroacetate **12**.

SCHEME 4[a]



[a] Reagents and conditions: (a) HCl, AcOH, rt, 1 h, 70%; (b) TFA, DCM, rt, 1 h, 44%; (c) LiOH, THF, rt, 1 h, 93%.

TABLE 1. nOe Data for Trifluoroacetate 12

irradiated proton	observed nOe (%)
$H_{12b,\alpha}$	H_{12} (7), $H_{1\alpha}$ (4)
$H_{1\alpha}$	$H_{1\beta}$ (30), $H_{12b,\alpha}$ (8)
$H_{1\beta}$	$H_{1\alpha}$ (30), $H_{3\beta}$ (4)
$H_{3\beta}$	$H_{3\alpha}$ (30), $H_{4\beta}$ (7), $H_{1\beta}$ (3)
$H_{4\beta}$	$H_{3\alpha}$ (5), $H_{3\beta}$ (4), H_5 (4)

TABLE 2. $^3J_{H,H}$ Couplings in Trifluoroacetate 12

coupled protons	dihedral (deg)[a]	calcd[b] $^3J_{H,H}$Hz	obsd $^3J_{H,H}$
$H_{12b,\alpha}-H_{1\alpha}$	−82.5	1.4	0
$H_{12b,\alpha}-H_{1\beta}$	163.0	10.6	8.3
$H_{4\beta}-H_{3\beta}$	75.3	0.9	1.8
$H_{4\beta}-H_{3\alpha}$	−37.4	6.5	5.2

[a] Measured in the minimum energy conformer (Figure 1). [b] Calculated with the Haasnoot−Altona equation.[18]

Interestingly, in the cyclization of **11** the ^1H NMR spectrum of the reaction mixture showed the major product **12**, to be present as just a single stereoisomer,[17] the stereochemistry of which was elucidated from nOe and ^3J proton coupling data as follows. The mutual nOe enhancements of the signals at 3.10 ppm ($H_{1\beta}$) and 3.23 ppm ($H_{3\beta}$) (Table 1) imply that these two protons are both axial, and hence the seven-membered ring has a half-chair conformation. Together with the other nOe data of Table 1, this makes H_{12b} axial and trans to equatorial H_4. These conclusions were supported by the coupling data for the two AMX three-spin systems of the azepine ring (Table 2): the large value of $^3J_{12b,1\beta} = 8.3$ Hz confirms the axial orientation of H_{12b}, and the small coupling of H_4 with vicinal protons shows its equatorial orientation. Furthermore, the observed coupling constants were in keeping with those given by the Haasnoot−Altona equation[18] for the minimum-energy conformation[19] calculated by molecular mechanics[20] for the proposed stereochemistry (Figure 1).

(16) Hendrickson, J. B.; Bergeron, R.; Sternbach, D. D. *Tetrahedron* **1975**, *31*, 2517−2521.

(17) The low isolated yield was due to partial decomposition of the trifluoroacetate during chromatography. Inspection of the ^1H NMR of the crude cyclization product did not show the presence of the cis stereoisomer.

(18) Haasnoot, C. A. G.; DeLeeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792. Calculations were performed using software provided by R. Stenutz at http://www.casper.organ.su.se/.

(19) The alternative distorted half-chair conformation with the trifluoroacetate group in a pseudoequatorial position is about 7 kcal/mol higher in energy.

(20) Molecular mechanics calculations were performed using the MM2 package of Chem-3D (CambridgeSoft Corporation, Cambridge, MA).

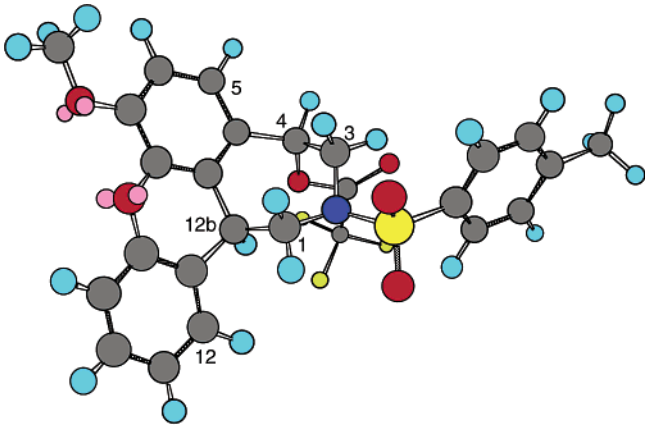


FIGURE 1. Minimum energy (MM2) conformer of **12**.

TABLE 3. Binding Properties (pIC_{50} Values) for the Reported Compounds[a]

	receptors					
compd	$A\alpha_{2A}$	$A\alpha_{2B}$	$A\alpha_{2C}$	D_{2L}	5-HT_{1A}	5-HT_7
1a	6.81	6.81	7.01	6.01	5.78	5.8
1b	6.83	6.74	6.74	<5[b]	5.31	5.9
1c	6.4	6.1	6.75	<5[b]	<5[b]	5.4
1d	<6[b]	<6[b]	<6[b]	<5[b]	<5[b]	<6[b]
7a	—[c]	—[c]	—[c]	—[c]	—[c]	<6[b]
7b	<7[b]	—[c]	—[c]	< 5[b]	—[c]	<6[b]
8b	<7[b]	—[c]	—[c]	< 5[b]	—[c]	<6[b]
10	6.2	6.3	6.06	5.54	6.12	7.05
13	<7[b]	<5[b]	<5[b]	<5[b]	<5[b]	<6[b]

[a] Binding affinities are shown as pIC_{50} values calculated from radioligand binding experiments performed in cell lines expressing human receptors for adrenergic α_{2A} ($A\alpha_{2A}$), adrenergic α_{2B} ($A\alpha_{2B}$), adrenergic α_{2C} ($A\alpha_{2C}$), dopamine$_2$ (long) (D_{2L}), serotonin$_{1A}$ (5-HT_{1A}), and serotonin$_7$ (5-HT_7). Briefly, frozen membranes of human receptor-transfected CHO cells ($A\alpha_{2A}$, $A\alpha_{2B}$, $A\alpha_{2C}$, D_{2L}, 5-HT_7) or L929 cells (5-HT_{1A}) were thawed, briefly homogenized, and diluted in assay buffer to an appropriate protein concentration optimized for specific and nonspecific binding. The compound was incubated with either [^{3}H]-rauwolscine ($A\alpha_{2A}$, $A\alpha_{2B}$, $A\alpha_{2C}$), [^{3}H]-spiperone (D_{2L}), [^{3}H]-8-OH-DPAT (5-HT_{1A}), or [^{3}H]-serotonin (5-HT_7), with membrane, in the presence and absence of cold excess of appropriate blank. Membrane-bound activity was collected by filtration method and measured, and competition binding curves containing at least eight concentrations were calculated using internal software (Insightful). [b] No significant binding was detected at these concentrations. [c] Not determined.

The biological activity of compounds **1a**−**d**, **7a**−**b**, **8b**, **10**, and **13** has been evaluated in a panel of receptor binding assays. We found that clavizepine (**1a**) shows affinity at the adrenergic α_{2A}, α_{2B}, and α_{2C}, dopaminergic D_2, and serotonergic 5-HT_{1A} and 5-HT_7 receptors, as summarized in Table 3. The binding at the α_2-adrenoceptors subtypes is retained in the *O*-methyl **1b** and *N*-demethyl **1c**[5] analogues, while the nonbasic *N*-tosyl derivative **1d**[5] leads to loss of affinity for the receptors tested. The same behavior was observed within the new series of D-ring-unsubstituted tosylamides **7a** and **13** and triflamides **7b** and **8b**, as they did not show any significant binding. However, the basic cinnamyl derivative **10** showed again moderate affinities for all three receptors tested, with the higher pIC_{50} value within the whole series of compounds for the 5-HT_7.

In conclusion, we have synthesized new analogues of clavizepine that have no D-ring substitutents. The very efficient key amination of an hydroxymethylxanthene intermediate by a Mitsunobu reaction using trifluoromethanesulfonamide allowed preparation of the tetracyclic chromeno-3-benzazepine **9** in just six steps and 38% overall yield. Furthermore, preparation of the 4-hydroxy clavizepine analogue **13** by cyclization of the sulfonamido aldehyde **11** took place stereoselectively providing the trans derivative. The synthetic *N*-cinnamyl derivative **10** showed a binding profile similar to that of clavizepine (**1a**), with higher affinity for the 5-HT_7 receptor.

Experimental Section

***N*-(2,2-Dimethoxyethyl), *N*-Trifluoromethanesulfonyl-9-aminomethyl-4-methoxy-9*H*-xanthene (6b).** Alcohol **5** (0.4 g, 1.65 mmol), *N*-(2,2-dimethoxyethyl)trifluoromethanesulfonamide (431 mg, 1.82 mmol), and triphenylphosphine (525 mg, 1.98 mmol) were dissolved in dry THF (5 mL) under Ar and cooled to 0 °C. Diethyl azodicarboxylate (313 μL, 1.98 mmol) was added dropwise, and the mixture was stirred for 5 h at room temperature. The THF was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2, washed with 1 M NaOH (2 × 30 mL) and then with brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded a residue that was column chromatographed (silica gel, 1:4 ethyl acetate/hexane) to afford **6b** (R_f 0.4, 610 mg, 80%) as a foam. IR (NaCl): 2939, 1739. ^{1}H NMR δ: 7.30−7.28 (m, 3H), 7.16−7.04 (m, 2H), 6.93−6.87 (m, 2H), 4.38 (t, J = 7.8 Hz, 1H), 4.29 (t, J = 5.3 Hz, 1H), 3.95 (s, 3H, OMe), 3.55 (bd, J = 7.8 Hz, 2H), 3.27 (s, 3H, OMe), 3.26 (s, 3H, OMe), 3.15−2.95 (broad, 2H). ^{13}C NMR δ: 152.8 (s), 148.6 (s), 142.3 (s), 129.2 (d), 129.1 (d), 124.3 (d), 123.9 (d), 123.6 (s), 122.5 (s), 120.8 (d), 120.2 (q, J = 323 Hz, SO_2CF_3), 117.5 (d), 111.5 (d), 103.4 (d, H*C*OMe$_2$), 56.9 (t), 56.5 (q, OMe), 55.1 (q, OMe), 54.9 (q, OMe), 51.4 (t), 39.9 (d). MS-CI (*m*/*z*): 462 (M + H$^+$, 1), 461 (M, 5), 430 (M − MeOH + H$^+$, 17), 398 (100), 211 (99). HRMS calcd for $C_{20}H_{22}NSO_6F_3$: 461.1120. Found: 461.1106.

7-Methoxy-2-trifluoromethanesulfonyl-2,12b-dihydro-1*H*-xantheno[9,1-*cd*]azepine (7b). Acetal **6b** (400 mg, 0.87 mmol), acetic acid (5 mL), and concentrated HCl (0.6 mL) were heated under Ar at 80 °C for 1 h and then 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 that was chromatographed (silica gel, 1:4 ethyl acetate/hexane) to afford **7b** (R_f 0.4, 289 mg, 84%), which was recrystallized from CH_2Cl_2/hexane. Mp: 166 °C. IR (NaCl): 1572, 1495, 1452. ^{1}H NMR δ: 7.42 (d, J = 7.3 Hz, 1H), 7.29 (dd, J = 8.5, 1.1 Hz, 1H), 7.16−6.97 (m, 2H), 6.91 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 10.5 Hz, 1H), 5.85 (d, J = 10.5 Hz, 1H), 4.74 (d, J = 13.9 Hz, 1H), 4.31 (d, J = 7.2 Hz, 1H), 3.93 (s, 3H, OMe), 3.70 (dd, J = 13.9, 7.2 Hz, 1H). ^{13}C NMR δ: 150.3 (s), 147.7 (s), 139.4 (s), 129.5 (d), 129.4 (d), 126.1 (s), 125.4 (d), 124.4 (d), 121.7 (s), 121.3 (d), 120.1 (q, J = 324 Hz, CF_3SO_2), 119.2 (s), 117.2 (d), 113.1 (d), 110.9 (d), 59.1 (t), 56.6 (q, OMe), 39.1 (d). MS (*m*/*z*): 397 (M$^+$, 32), 264 (M − CF_3SO_2, 100), 249 (10), 236 (18), 221 (38). HRMS calcd for $C_{18}H_{14}F_3NO_4S$: 397.0596. Found: 397.0591.

7-Methoxy-2-trifluoromethanesulfonyl-2,3,4,12b-tetrahydro-1*H*-xantheno[9,1-*cd*]azepine (8b). Compound **7b** (309 mg, 0.78 mmol) and 10% Pd/C (100 mg) were stirred in THF (14 mL) under 1 atm of H_2 for 12 h. Filtration through Celite and evaporation of the solvent in vacuo then afforded sulfonamide **8b** (280 mg, 90%), which was taken into ether/hexane. Mp: 215 °C. IR (NaCl): 1577, 1498, 1458, 1376. ^{1}H NMR δ: 7.43 (d, J = 7.1 Hz, 1H), 7.29−7.23 (m, 1H), 7.16−7.10 (m, 2H), 6.83 (d, J = 8.2 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 4.49 (d, J = 9.1 Hz, 1H), 4.30−4.22 (m, 2H), 3.93 (s, 3H, OMe), 3.30 (dd, J = 14.3, 9.3 Hz, 1H), 3.20 (dd, J = 14.3, 12.1 Hz, 1H), 3.03 (t, J = 12.7 Hz, 1H), 2.93 (dd, J = 15.1, 5.5 Hz, 1H). ^{13}C NMR δ: 150.5 (s), 147.4 (s), 140.2 (s), 132.0 (s), 130.0 (d), 129.3 (d), 124.3 (d), 123.8 (d), 122.8 (s), 120.3 (q, J = 323 Hz, SO_2CF_3), 119.8 (s), 117.2 (d), 110.8 (d), 59.3 (t), 56.6 (q, OMe), 49.6 (t), 40.4 (d), 37.6 (t). MS (*m*/*z*): 399 (M$^+$, 12), 266 (M − CF_3SO_2, 100), 239 (16), 225 (28), 209 (78). HRMS calcd for $C_{18}H_{16}F_3NO_4S$: 399.0752. Found: 399.0739.

7-Methoxy-2,3,4,12b-tetrahydro-1*H*-xantheno[9,1-*cd*]azepine (9). Method B. Triflamide **8b** (50 mg, 0.12 mmol) was dissolved in dry THF (7 mL) under Ar, Red-Al solution (65% in toluene, 195 μL, 0.62 mmol) was added, and the mixture was heated at 100 °C for 1 h. The resulting solution was cooled to 0 °C, NH_4Cl solution was added, the THF was removed in vacuo, and the residue was dissolved in CH_2Cl_2. This solution was washed with water and dried over anhydrous Na_2SO_4, and evaporation of the solvent in vacuo then afforded a residue that when column chromatographed (silica gel, 94:6 CH_2Cl_2/MeOH) afforded amine **9** (R_f 0.3, 28 mg, 85%). IR (NaCl): 3338 (NH), 1578, 1493, 1449. ^{1}H NMR δ: 7.29 (d, J = 7.5 Hz, 1H), 7.23−7.12 (m, 2H), 7.03 (td, J = 7.5, 1.8 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 4.32 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H, OMe), 3.43−3.20 (m, 2H), 3.12−3.08 (m, 1H), 2.98 (dd, J = 13.2, 1.6 Hz, 1H), 2.75−2.60 (m, 2H), 2.73 (bs, NH). ^{13}C NMR δ: 150.5 (s), 146.7 (s), 140.0 (s), 134.5 (s), 129.7 (d), 128.3 (d), 124.4 (s), 123.6 (d), 123.0 (d), 122.5 (s), 116.9 (d), 110.0 (d), 59.9 (t), 56.5 (q), 48.3 (t), 41.5 (d), 39.0 (t). MS (*m*/*z*): 267 (M^+, 39), 237 (52), 225 (100), 209 (28). HRMS calcd for $C_{17}H_{17}NO_2$: 267.1260. Found: 267.1256.

7-Methoxy-2-[(*E*)-3-phenylprop-2-enyl]-2,3,4,12b-tetrahydro-1*H*-xantheno[9,1-*cd*]azepine (10). Cinnamaldehyde (92 μL, 0.72 mmol) was added to a solution of amine **9** (190 mg, 0.71 mmol) in dry MeOH (25 mL) followed after 30 min by sodium cyanoborohydride (142 mg, 2.1 mmol). After 14 h of being stirred at room temperature, some drops of NH_4Cl solution were added. The solvent was evaporated, the residue was dissolved in CH_2Cl_2, and this solution was washed with water and dried with anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded a residue that was purified by column chromatography (silica gel, 200:1 CH_2Cl_2/MeOH) affording amine **10** (R_f 0.2, 136 mg, 50%), which was recrystallized from CH_2Cl_2/hexane. Mp: 125 °C. IR (NaCl): 1579. ^{1}H NMR δ: 7.60−7.09 (m, 8H), 7.03 (td, J = 8.0, 1.5 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 6.53 (d, J = 15.8 Hz, 1H), 6.33 (dt, J = 15.8, 6.6 Hz, 1H), 4.48 (d, J = 9.2 Hz, 1H), 3.92 (s, 3H, OMe), 3.36 (d, J = 6.6 Hz, 2H), 3.17−3.15 (m, 3H), 2.72 (dd, J = 14.8, 6.2 Hz, 1H), 2.64 (dd, J = 12.5, 9.6 Hz, 1H), 2.24 (t, J = 12.0 Hz, 1H). ^{13}C NMR δ: 150.4 (s), 146.3 (s), 139.6 (s), 136.8 (s), 134.3 (s), 133.2 (d), 129.6 (d), 128.6 (d), 127.9 (d), 127.5 (d), 126.6 (d), 126.3 (d), 124.2 (s), 123.3 (d), 122.4 (s), 122.3 (d), 116.5 (d), 109.7 (d), 66.7 (t), 61.3 (t), 56.2 (q, OMe), 55.0 (t), 37.5 (d), 35.3 (t). MS (*m*/*z*): 383 (M^+, 26), 266 (M − CH_2CH═CHPh, 100), 237 (40), 225 (42), 209 (90). HRMS calcd for $C_{26}H_{25}NO_2$: 383.1885. Found: 383.1882.

***N*-(Formylmethyl), *N*-Tosyl-9-aminomethyl-4-methoxy-9*H*-xanthene (11).** A mixture of acetal **6a** (370 mg, 0.77 mmol), glacial acetic acid (6 mL), water (6 mL), and concentrated HCl (2 mL) was stirred at room temperature under Ar for 1 h, 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 dryness. Chromatography of the residue (silica gel, 3:7 ethyl acetate/hexane) afforded aldehyde **11** as a foam (R_f 0.4, 234 mg, 70%). IR (NaCl): 1730 (CHO), 1575, 1484. ^{1}H NMR δ: 9.15 (s, 1H, CHO), 7.64 (d, J = 8.3 Hz, 2H), 7.38−7.21 (m, 4H), 7.16−7.04 (m, 3H), 6.97 (dd, J = 7.7, 1.5 Hz, 1H), 6.88 (dd, J = 7.8, 1.5 Hz, 1H), 4.42 (t, J = 7.4 Hz, 1H), 3.93 (s, 3H, OMe), 3.34 (s, 2H, CH_2CHO), 3.21 (d, J = 7.4 Hz, 2H), 2.41 (s, 3H, Me). ^{13}C NMR δ: 197.8 (d), 152.5 (s), 148.5 (s), 144.5 (s), 142.0 (s), 135.4 (s), 130.3 (d), 129.6 (d), 128.9 (d), 127.9 (d), 124.2 (d), 123.9 (d), 123.8 (s), 122.7 (s), 121.2 (d), 117.2 (d), 111.4 (d), 59.9 (t), 57.8 (t), 56.4 (q, OMe), 40.7 (d), 21.9 (q, Me). MS (FAB) (*m*/*z*): 438 (M + H^+, 3), 355 (6), 309 (17), 238 (24), 231 (64). HRMS calcd for $C_{24}H_{24}NO_5S$: 438.1375. Found: 438.1368.

(4*S,12b*S**)-2,3,4,12b-Tetrahydro-4-trifluoroacetoxy-7-methoxy-2-tosyl-1*H*-xantheno[9,1-*cd*]azepine (12).** TFA (1.5 mL) was added to a solution of aldehyde **11** (225 mg, 0.51 mmol) in CH_2Cl_2 (4 mL), and the mixture was stirred at room temperature for 1 h, cooled to 0 °C, and treated with a saturated aqueous solution of $NaHCO_3$. The aqueous phase was separated and extracted with CH_2Cl_2, the combined organic phases were washed with brine and then dried over anhydrous Na_2SO_4, the CH_2Cl_2 was removed in vacuo, and the residue was rapidly column chromatographed (silica gel, 8:1 CH_2Cl_2/hexane), which afforded **12** (R_f 0.7, 121 mg, 44%) as an amorphous solid. IR (NaCl): 2932, 1782 (CO), 1576, 1494. ^{1}H NMR δ: 7.63 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 7.0 Hz, 1H), 7.27−7.25 (m, 3H), 7.15−7.12 (m, 2H), 6.98 (d, J = 8.3 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 6.00 (dd, J = 5.2, 1.8 Hz, 1H), 4.84 (d, J = 8.3, Hz, 1H), 4.40 (dd, J = 14.6, 5.2 Hz, 1H), 4.13 (d, J = 13.8 Hz, 1H), 3.92 (s, 3H, OMe), 3.23 (dd, J = 14.6, 1.8 Hz, 1H), 3.10 (dd, J = 13.8, 8.3 Hz, 1H). ^{13}C NMR δ: 157.0 (q, J = 43 Hz, CO_2CF_3), 150.0 (s), 149.8 (s), 144.0 (s), 140.4 (s), 136.9 (s), 130.3 (d), 129.9 (d), 129.1 (d), 127.2 (d), 126.4 (s), 126.3 (d), 124.3 (d), 123.1 (s), 119.9 (s), 117.0 (d), 114.9 (q, J = 286 Hz, CF_3), 110.0 (d), 79.8 (d), 58.2 (t), 56.5 (q, OMe), 49.2 (t), 37.8 (d), 21.8 (q, Me). MS (FAB) (*m*/*z*): 534 (M + H^+, 28), 420 (M − $OCOCF_3$, 100). HRMS calcd for $C_{26}H_{23}F_3NO_6S$: 534.1198. Found: 534.1188.

(4*S,12b*S**)-2,3,4,12b-Tetrahydro-7-methoxy-2-tosyl-1*H*-xantheno[9,1-*cd*]azepin-4-ol (13).** Trifluoroacetate **12** (119 mg, 0.22 mmol) was dissolved in THF (6 mL), a solution of $LiOH·H_2O$ (130 mg, 3.1 mmol) in H_2O (2 mL) was added, and the mixture was vigorously stirred for 1 h. The THF was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2. This solution was washed with 10% aqueous HCl, the aqueous phase was separated and extracted with CH_2Cl_2, the combined organic phases were washed with water and then dried over anhydrous Na_2SO_4, and the CH_2Cl_2 was removed in vacuo. Column chromatography of the residue (CH_2Cl_2) afforded **13** (R_f 0.2, 98 mg, 93%), which was recrystallized from ether/hexane. Mp 163 °C (dec). IR (NaCl): 3470 (OH), 1577, 1493. ^{1}H NMR δ: 7.66 (d, J = 8.3 Hz, 2H), 7.04 (d, J = 7.0 Hz, 1H), 7.28−7.21 (m, 3H), 7.14−6.91 (m, 2H), 6.84 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 5.09 (d, J = 9.5 Hz, 1H), 4.86 (dd, J = 4.8, 3.1 Hz, 1H), 4.26 (d, J = 13.5 Hz, 1H), 4.29−4.22 (m, 1H), 3.90 (s, 3H, OMe), 2.97 (d, J = 14.0 Hz, 1H), 2.96 (dd, J = 13.5, 9.5 Hz, 1H), 2.80 (d, J = 3.1 Hz, 1H, OH), 2.39 (s, 3H). ^{13}C NMR δ: 150.2 (s), 148.5 (s), 143.9 (s), 140.2 (s), 136.6 (s), 132.6 (s), 130.2 (d), 130.1 (d), 128.8 (d), 127.3 (d), 124.2 (d), 124.1 (d), 122.5 (s), 120.6 (s), 116.9 (d), 109.8 (d), 74.7 (d), 58.7 (t), 56.4 (q, OMe), 52.2 (t), 37.3 (d), 21.9 (q). MS (FAB) (*m*/*z*): 438 (M + H^+, 24), 437 (M, 19), 420 (M − H_2O + H^+, 100). HRMS calcd for $C_{24}H_{23}NO_5S$: 437.1297. Found: 437.1304.

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Supporting Information Available: Experimental procedures and characterization data for **5, 6a, 7a, 8a, 9** (Method A) and *N*-(2,2-dimethoxyethyl)trifluoromethanesulfonamide. Copies of the ^{1}H NMR and ^{13}C NMR spectra for compounds **3**, **4**, **5**, **6a**, **6b**, **7a**, **7b**, **8a**, **8b**, **9**, **10**, **11**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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