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# Synthesis of Pyrrolo- and Pyrido[1,2-*a*]xanthene [1,9-*de*]azepines: A Study of the Azepine Ring Construction

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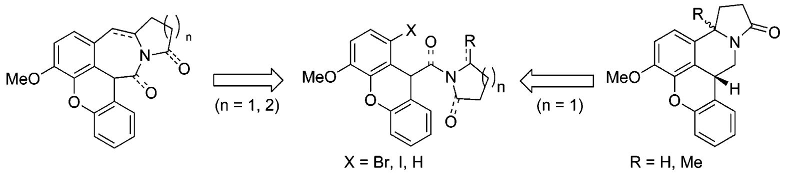
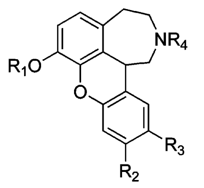


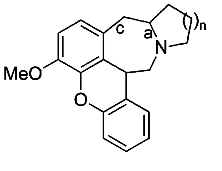
Pentacyclic pyrrolo- and pyrido[1,2-*a*]xanthene[1,9-*de*]azepines were synthesized in various oxidation states by assembling the azepine ring following two strategies: 7-*endo-trig* cyclization of the aryl radical derived from a $\gamma$-methylene lactam and cyclodehydration of aldehydes. Other strategies examined (Heck reaction and intramolecular acylation) did not afford azepines, but six-membered nitrogenated rings.

## Introduction

(−)-Clavizepine (**1a**) is a unique natural product isolated from *Corydalis claviculata* (L.) DC in 1986[1] and soon afterward found in *Sarcocapnos crassifolia* subsp. *speciosa*,[2] both of them plants belonging to the Fumariaceae family. It is the only known alkaloid with a xanthene[1,9-*de*]azepine skeleton. It binds to adrenergic $\alpha_{2A}$, $\alpha_{2B}$, and $\alpha_{2C}$ receptors, dopaminergic D$_{2L}$ receptors, and serotonergic 5-HT$_{1A}$ and 5-HT$_7$ receptors; the analogue with the highest pIC$_{50}$ for binding to 5-HT$_7$ is **1b**.[3] These activities are probably due to the presence of the biologically active 1-aryl-3-benzazepine pharmacophore,[4] which in these molecules is rigidified by the ether bridge connecting both aryl units. In this paper, we describe synthetic studies directed toward the preparation of the pentacyclic analogues **2** and **3**, incorporating a fused pyrrole and pyrido rings on azepine bond *a*. Here, we report the results of a study of what, a priori, were regarded as several possible methods for constructing the bond *c* from precursors with a variety of different oxidation states.



**1a**, R$_1$=H, R$_2$=R$_3$=OMe, R$_4$=Me
**1b,** R$_1$=Me, R$_2$=R$_3$=H, R$_4$=cinnamyl



**2,** n = 1
**3**, n = 2

## Results and Discussion

We first addressed the synthesis of the pyrrolo derivative **2a**, assembling the seven-membered ring by 7-*endo-trig* cyclization of the aryl radical derived from the $\gamma$-methylene lactam **7b**. Since aryls retain their aromaticity during radical formation they afford very reactive $\sigma$-radicals that rapidly attack unsaturated neutral carbon atoms. The 7-*endo-trig* cyclization consisting in intramolecular addition of an aryl radical to an enamide double bond, discovered independently by ourselves and by Rigby,[5] has become an established regioselective route to benz[*d*]indeno-

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(1) Boente, J. M.; Castedo, L.; Domínguez, D.; Ferro, M. C. *Tetrahedron Lett.* **1986**, *27*, 4077−78.

(2) Castedo, L.; López, S.; Rodríguez de Lera, A.; Villaverde, M. C. *Phytochemistry* **1988**, *28*, 251−57.

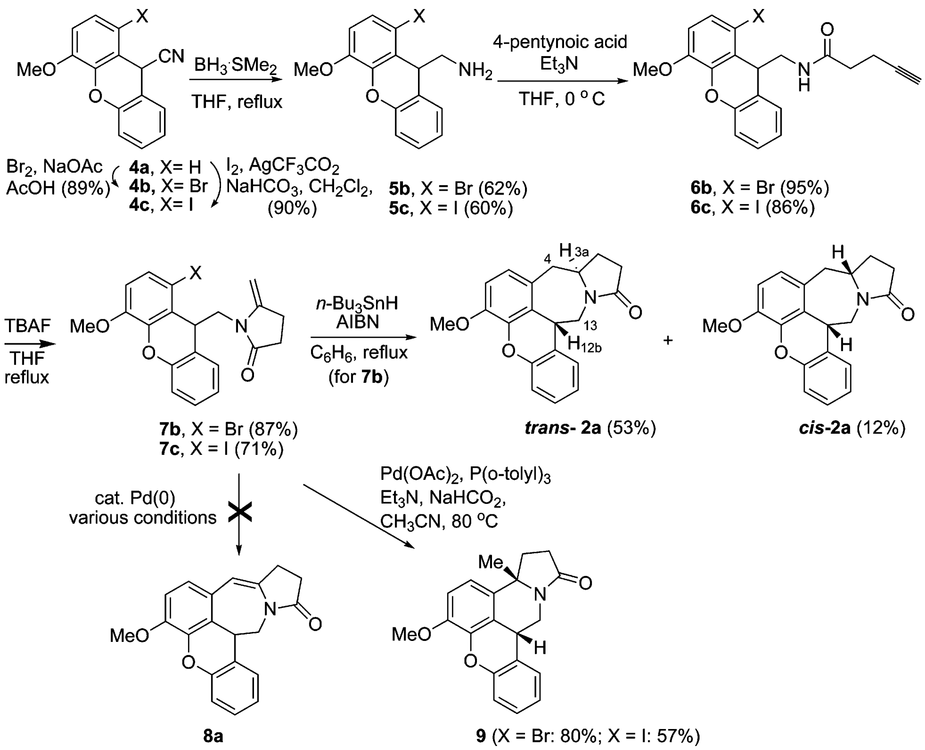
(3) de la Fuente, M. C.; Pullan, S. E.; Biesmans, I.; Domínguez, D. *J. Org. Chem.* **2006**, *71*, 3963−66

(4) For recent work on the pharmacology of 1-aryl-3-benzazepines, see: (a) Williams, S.; Mmbaga, N.; Chirwa, S. *Neurosci. Lett.* **2006**, *402*, 46−50. (b) Fujita, S.; Lee, J.; Kiguchi, M.; Uchida, T.; Cools, A. R.; Waddington, J. L.; Koshikawa, N. *Eur. J. Pharmacol.* **2006**, *538*, 94−100. (c) Ryman-Ramussen,. P.; Nichols, D. E.; Mailman, R. B. *Mol. Pharmacol.* **2005**, *68*, 1039−48. (d) Krull, O.; Wunsch, B. *Bioorg. Med. Chem.* **2004**, *12*, 1439−51. (e) Jin, L-Q.; Goswami, S.; Cai, G.; Zhen, X.; Friedman, E. *J. Neurochem.* **2003**, *85*, 378−86.

(5) (a) Rigby, J. H.; Qabar, M. N. *J. Org. Chem.* **1993**, *58*, 4473−75. (b) For a related 6-*endo-trig* intramolecular addition of an aryl radical to an enamide, see: Schultz, A. G.; Holoboski, M. A. Smyth, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 7904−05.

10.1021/jo701568w CCC: $37.00

**SCHEME 1**



[1,2-*b*]azepines,[6] isoindolo[3]benzazepines,[7] and other 3-benzazepines.[8]

Our starting compound was 4-methoxy-9*H*-xanthene-9-carbonitrile (**4a**).[9] Regioselective bromination or iodination of **4a**, followed by reduction with borane, provided the aminomethyl xanthenes **5b** (62%) and **5c** (60%), which were converted to amides **6b** and **6c** by condensation with 4-pentynoic acid. The $\gamma$-methylene lactams **7b** and **7c** were prepared by TBAF-promoted 5-*exo-dig* cyclization of the acetylenic amides **6b** and **6c** following the procedure reported by Jacobi et al. (Scheme 1).[10]

The radical cyclization of **7b** afforded a mixture of two main products, which after separation by column chromatography were identified as the diastereomeric azepines ***trans***- and ***cis*-2a**, obtained in 53% and 12% yield, respectively. Following $^1$H, $^{13}$C/DEPT, COSY, and HMQC experiments identifying the most significant proton NMR signals of these compounds (see Table 1 in the Suporting Information), the relative configuration of $H_{12b}$ and $H_{3a}$ was deduced by NOE experiments: irradiation of the multiplet signal of $H_{3a}$ ($\delta$: 3.50−3.64 ppm) in the major compound resulted in a 3% enhancement of the $H_{13\alpha}$ signal ($\delta$: 2.94 ppm) that was only compatible with ***trans*-2a**, while the ***cis-2a*** stereochemistry of the minor isomer was confirmed by the strong NOE effects between the four protons located on the $\beta$ face of the molecule, which are very close together in the boat-shaped minimum-energy conformation. Also, the experimental $^3J$ proton couplings agree well with those given by the Haasnoot−Altona equation[11] for the calculated[12] minimum-energy conformations of the two epimers (Table 1 in the Supporting Information).

The lack of stereoselectivity and moderate yield of the above radical-mediated reaction persuaded us to consider a Heck-type coupling reaction of bromide **7b** or iodide **7c**. 3-Benzazepines have frequently been prepared by 7-*exo* cyclization using intramolecular Heck reactions,[13] but the corresponding 7-*endo* cyclization has only been reported for a few α-substituted enamides.[14] Our cyclic enamides **7b** and **7c** failed to afford the desired product **8a**. Heating them in toluene with Pd$_2$(dba)$_3$, K$_2$CO$_3$, and P(*o*-tolyl)$_3$ gave complex mixtures from which only a 10−20% yield of the 6-*exo* cyclization product **9** could be isolated. Jeffery conditions (Pd(OAc)$_2$, NaHCO$_3$, *n*-Bu$_4$NBr, 3 Å molecular sieves, DMF, 110 °C), which have been reported to favor *endo* products, again led to **9** (25%). Since this

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[6] Fidalgo, J.; Castedo, L.; Domínguez, D. *Tetrahedron Lett.* **1993**, *34*, 7317−18.

[7] (a) Rodríguez, G.; Cid, M. M; Saá, C.; Castedo, L.; Domínguez, D. *J. Org. Chem.* **1996**, *61*, 2780−82. (b) Cid, M. M.; Domínguez, D.; Castedo, L.; Vázquez-López, E. M. *Tetrahedron* **1999**, *55*, 5599−10.

[8] (a) Gibson, S. E. (neé Thomas); Guillo, N.; Tozer, M. J. *J. Chem. Soc., Chem. Commun.* **1997**, 637−38. (b) Taniguchi, T.; Iwasaki, K.; Uchiyama, M.; Tamura, O.; Ishibashi, H. *Org. Lett.* **2005**, *7*, 4389−90. (c) Taniguchi, T.; Ishita, A.; Uchiyama, M.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 1922−25.

[9] de la Fuente, M. C.; Domínguez, D. *Tetrahedron* **2004**, *60*, 10019−28.

[10] Jacobi, P. A.; Brielmann, H. L.; Hauck, S. I. *J. Org. Chem.* **1996**, *61*, 5013−23.

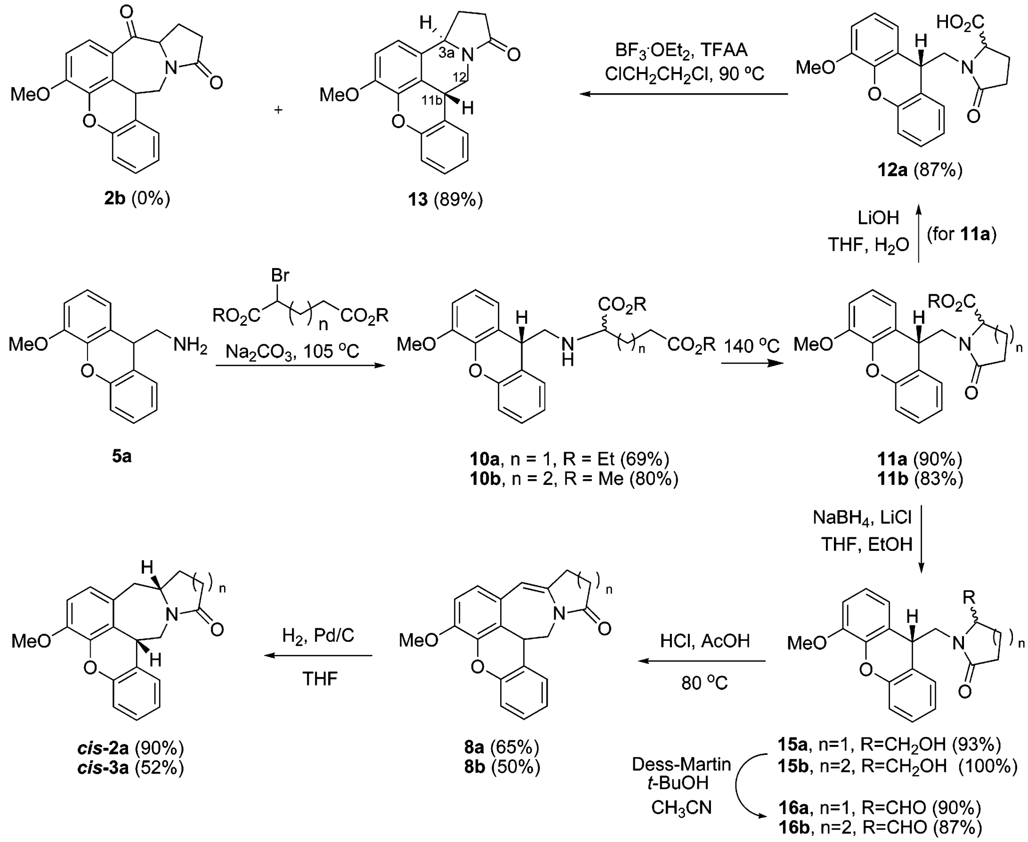
[11] Haasnoot, C- A. G.; DeLeeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−92.

[12] Molecular mechanics calculations were performed using the MM2 package of Chem-3D (CambridgeSoft Corp., Cambridge, MA).

[13] (a) Tietze, L. F.; Schimpf, R. *Synthesis* **1993**, 876−80. (b) Tietze, L. F.; Thede, K.; Schimpf, R.; Sannicolo, F. *J. Chem. Soc., Chem. Commun.* **2000**, 583−84. (c) Worden, S. M.; Mapitse, R.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6011−14. (d) Fishwick, C. W. G.; Grigg, R.; Sridharan, V.; Virica, J. *Tetrahedron* **2003**, *59*, 4451−68. (e) Smith, B. M.; Smith, J. M.; Tsai, J. H.; Schultz, J. A.; Gilson, C. A.; Estrada, S. A.; Chen, R. R.; Park, D. M.; Prieto, E. B.; Gallardo, C. S.; Sengupta, D.; Thomsen, W. J.; Saldana, H. R.; Whelan, K. T.; Menzaghi, F.; Webb, R. R.; Beeley, N. R. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1467−70. (f) Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Biomol. Chem.* **2007**, *5*, 143−50.

[14] (a) Gibson, S. E. (neé Thomas); Middleton, R. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1743−44. (b) Gibson, S. E. (neé Thomas); Guillo, N.; Middleton, R. J.; Thuilliez, A.; Tozer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 447−55.

**SCHEME 2**



compound presumably arose as a result of hydride ion capture by the alkylpalladium derivative generated by 6-*exo* cyclization, we envisaged that its yield might be increased by carrying out the Heck reaction under reducing conditions; in accordance with these expectations, addition of sodium formate to a mixture of **7b** or **7c**, Pd(OAc)$_2$, Et$_3$N, and P(*o*-tolyl)$_3$ in refluxing acetonitrile afforded compound **9** in 80% or 57% yield, respectively (Scheme 1).[15] This cyclization was stereoselective, and the relative configuration of the two stereocenters was shown by NOE experiments in which irradiation of the benzylic proton at 4.55 ppm caused a 6% enhancement of the methyl signal and irradiation of the methyl group at 1.53 ppm gave a 5% enhancement at 4.55 ppm.

Thus, under radical conditions, bromide **7b** affords the corresponding azepine in moderate yield as a mixture of stereoisomers, while the Heck reactions of both bromide **7b** and iodide **7c** afford a six-membered ring as the result of the alternative 6-*exo-trig* cyclization mode. The discrepancy between these results and those reported by Gibson et al. for similar systems[8a] highlights the importance of substrate structure for the outcome of these reactions.

We next considered an approach to azepinone **2b** based on intramolecular acylation in the pyrrolidone carboxylic acid **12a**, which was prepared by alkylation of amine **5a** with diethyl 2-bromopentanedioate,[16] thermal cyclization of diastereomeric mixture **10a** to the lactam **11a**, and hydrolysis of the latter by LiOH in THF/H$_2$O. However, treatment of **12a** with BF$_3$·OEt$_2$/TFAA,[17] instead of affording **2b**, produced the pentacyclic isoquinoline **13**, activation of the carboxyl having been followed by fast decarbonylation to an acyliminium intermediate preceding the electrophilic attack (Scheme 2).[18] The stereochemistry of **13** was deduced from the results of NOE experiments in which irradiation at 4.81 ppm (H$_{3a}$) caused a 3.5% enhancement at 3.07 ppm (H$_{12\alpha}$), but H$_{3a}$ was unaffected when H$_{11b}$ was irradiated (and vice versa). With other acid conditions, **12a** was recovered (SnCl$_4$/TFAA)[19] or product **13** was again obtained (PPA).[20]

We then tried intramolecular acylation of **12c** (Scheme 3), a positional isomer of **12a** in which the intermediate acyl cation would be stabilized by the nearby carbonyl. Carboxy amide **12c** was prepared from nitrile **4a** by hydrolysis to acid **14** followed by condensation with L-methyl prolinate and final basic hydrolysis of the resulting epimeric mixture of esters **11c** (Scheme 3). However, cyclization of **12c** with SnCl$_4$/TFAA was also unsuccessful, affording only starting material, and when PPA was used no single product could be isolated after workup. The use of aluminum trichloride following oxalyl chloride treatment[21] led to decomposition. These results show that azepinediones such as **2b** and **2c** cannot be prepared by

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[15] Burns, B.; Grigg, R.; Ratananukul, P.; Sridharan, V.; Stevenson, P.; Woraku, T. *Tetrahedron Lett.* **1988**, *29*, 4329−32.

[16] Schwenk, E.; Papa, D. *J. Am. Chem. Soc.* **1948**, *70*, 3626−27.

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[18] Generation of iminium ions from acid chlorides derived from α-amino acids has been previously reported: (a) Rehman, M. A.; Proctor, G. R. *J. Chem. Soc (C)* **1967**, 58−61. (b) Dean, R. T.; Padett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448−49.

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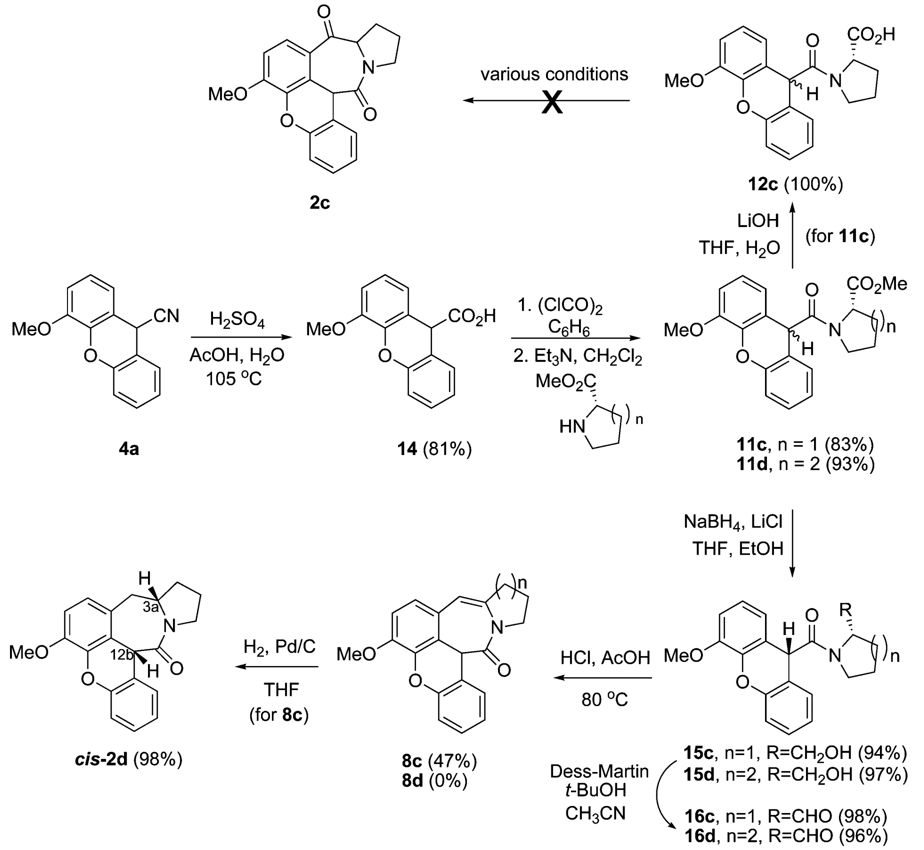
[20] Yasuda, S.; Yamada, T.; Hanaoka, M. *Tetrahedron Lett.* **1986**, *27*, 2023−26.

[21] Belanger, P. C.; Atkinson, J. G.; Rooney, C. S.; Britcher, S. F.; Remy, D. C. *J. Org. Chem.* **1983**, *48*, 34−41.

**SCHEME 3**



intramolecular acylation independently of the position of the amide carbonyl.

Since the Heck reaction discussed above had failed to afford unsaturated azepine **8a** from $\gamma$-methylene lactams **7b**,**c** we decided to try the cyclodehydration of the more reactive substrate aldehyde **16a**,[22] which was prepared from ester **11a** by reduction to alcohol **15a** followed by oxidation with Dess−Martin periodinane (Scheme 2). Gratifyingly, treatment of **16a** with HCl in hot acetic acid afforded the cyclized product **8a** in 65% yield after chromatographic purification (Scheme 2), and hydrogenation of the double bond gave a 90% yield of azepine ***cis*-2a**, the minor product of the radical route (Scheme 1). The same reaction sequence also led from the higher homologue **11b** to pyridoazepine **8b** and its reduction product ***cis*-3a** (Scheme 2), the required ester **11b** having been prepared by alkylation of amine **5a** with 2-bromohexanedioic acid dimethyl ester[23] followed by thermal cyclization to the lactam (Scheme 2). The *cis* stereochemistry of azepine **3a** was deduced from the 12.5% increase in the intensity of the $H_{4a}$ signal that was observed upon irradiation of $H_{13b}$.

To apply the cyclodehydration method of Scheme 2 to the synthesis of the azepinones **8c** and **8d**, in which the carbonyl is borne by the azepine ring, we prepare the required aldehydes **16c** and **16d** from the amides **11c** and **11d** (Scheme 3). Under standard acidic conditions, pyrrolidino-2-carbaldehyde **16c** cyclized to the desired azepinone **8c** (which was then reduced to what a 4.6% NOE between $H_{12b}$ and $H_{3a}$ showed to be ***cis*-2d**), but the piperidine analogue unexpectedly underwent hydrolysis to acid **14** instead.

Finally, we prepared pyrrolazepinone **19** by Friedel−Crafts cyclization[24] of acid **18** (Scheme 4), which was obtained by a two-step sequence: first, the pyrrole ring was formed on the amino nitrogen of **5b** by treatment with 2,5-dialkoxytetrahydrofuran, then pyrrole **17** was converted into the corresponding lithium salt with *n*-BuLi, $CO_2$ was passed through the solution, and final acidification yielded **18**. Compound **19** was obtained in 90% yield by electrophilic cyclization of **18** by treatment with PPE.[25]

To summarize, in this work, we evaluated a priori alternatives for the assembly of pentacyclic pyrrolo- and pyridoxanthenoazepines. Radical cyclizations, Heck reactions, and electrophilic cyclodehydration gave access to final targets in a variety of different oxidation states, but intramolecular acylation appeared to be a useful approach only in the case of aromatic pyrrolo derivatives like **19**.

## Experimental Section

***N*-[(1-Bromo-4-methoxy-9*H*-xanthen-9-yl)methyl]-4-pentynamide (6b).** A solution of 4-pentynoic acid (320 mg, 3.16 mmol) in dry THF (16 mL) was cooled to 0 °C, and $Et_3N$ (478 $\mu$L, 3.43 mmol) and isobutyl chloroformate (455 $\mu$L, 3.43 mmol) were added. The mixture was stirred for 1 h, and amine **5b** (1 g, 3.12 mmol) in

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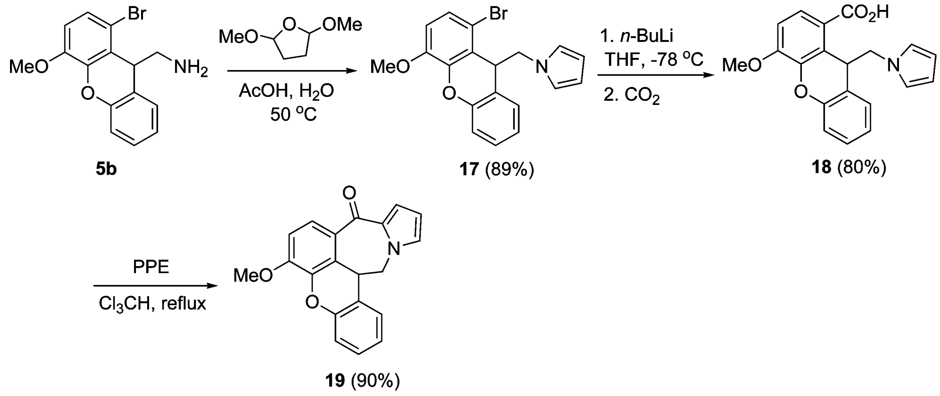
(22) For related examples of this type of cyclization, see: (a) Bousquet, T.; Fleury, J-F.; Daïch, A.; Netchitaïlo, P. *Tetrahedron* **2006**, *62*, 706−15. (b) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *Tetrahedron* **2000**, *56*, 1491−99.

(23) Baker, B. R.; Querry, M. V.; Bernstein, S.; Safir, S. R.; Subbarow, Y. *J. Org. Chem.* **1947**, *12*, 167−73.

(24) Girard, Y.; Atkinson, J. G.; Belanger, P. C.; Fuentes, J. J.; Rokach, J.; Rooney, C. Stanley; R., David C.; Hunt, C. A. *J. Org. Chem.* **1983**, *48*, 3220−34.

(25) Cava, M. P.; Lakshmikantham, M. V.; Mitchell, M. J. *J. Org. Chem.* **1969**, *34*, 2665−67.

**SCHEME 4**



THF (10 mL) was added. After the mixture was stirred for 4 h at 0 °C, the solvent was removed under reduced pressure, the residue was partitioned between $CH_2Cl_2$ and water, and the organic layer was washed with water, dried with $Na_2SO_4$, filtered, and concentrated. Purification by flash chromatography ($SiO_2$, 99:1 $CH_2Cl_2$/MeOH) gave **6b** (1.17 g, 95%) which was taken into ether/hexane and filtered out: mp 156 °C; IR (KBr) 3419 (NH), 3293 (HC≡), 1643 (CO) cm$^{-1}$; $^1$H NMR $\delta$ 7.32−7.21 (m, 4H), 7.13 (ddd, $J$ = 7.5, 6.2, 2.2 Hz, 1H), 6.76 (d, $J$ = 8.8 Hz, 1H), 5.58 (t, $J$ = 5.8 Hz, 1H, NH), 4.46 (t, $J$ = 5.8 Hz, 1H), 3.92 (s, 3H, OMe), 3.64 (ddd, $J$ = 13.4, 6.2, 5.6 Hz, 1H), 3.45 (ddd, $J$ = 13.4, 6.2, 6.2 Hz, 1H), 2.46−2.36 j(m, 2H), 2.32−2.26 (m, 2H), 1.92 (t, $J$ = 2.6 Hz, 1H); $^{13}$C NMR/ DEPT $\delta$ 171.2 (CO), 152.5 (C), 148.1 (C), 143.5 (C), 129.2 (CH), 128.8 (CH), 127.2 (CH), 124.5 (CH), 123.9 (C), 122.9 (C), 117.0 (CH), 114.2 (C), 112.2 (CH), 83.4 (C), 69.6 (CH), 56.7 (OMe), 45.6 ($CH_2$), 40.4 (CH), 35.6 ($CH_2$), 14.9 ($CH_2$); MS (FAB) ($m/z$) 402 [(M + 2 + H)$^+$, 99], 400 [(M + H)$^+$, 100]; HRMS (FAB) calcd for $C_{20}H_{19}BrNO_3$ [(M + H)$^+$] 400.0548, found 400.0552.

**1-[(1-Bromo-4-methoxy-9*H*-xanthen-9-yl)methyl)]-5-methylenepyrrolidin-2-one (7b).** TBAF (4.5 mL, 4.5 mmol, 1 M in THF) was added to a solution of amide **6b** (900 mg, 2.25 mmol) in dry THF (22 mL), and the mixture was heated at 100 °C for 10 h. The solvent was evaporated, the residue was partitioned between $CH_2Cl_2$ and water, and the organic layer was washed with water, dried with $Na_2SO_4$, filtered, and concentrated. Purification by flash chromatography ($SiO_2$, 2:3 EtOAc/hexane) gave **7b** (781 mg, 87%), which was recrystallized in ether/hexane: mp 161 °C; IR (KBr) 1720 (CO), 1700 cm$^{-1}$; $^1$H NMR $\delta$ 7.32−7.17 (m, 3H), 7.06−7.04 (m, 2H), 6.77 (d, $J$ = 8.8 Hz, 1H), 4.64 (dd, $J$ = 8.8, 6.6 Hz, 1H), 4.34 (d, $J$ = 1.9 Hz, 1H), 4.08 (d, $J$ = 1.9 Hz, 1H), 3.94 (s, 3H, OMe), 3.71 (dd, $J$ = 13.5, 8.8 Hz, 1H), 3.57 (dd, $J$ = 13.5, 6.6 Hz, 1H), 2.64−2.62 (m, 2H), 2.36−2.28 (m, 2H); $^{13}$C NMR/ DEPT $\delta$ 176.1 (CO), 152.7 (C), 148.3 (C), 146.9 (C), 143.8 (C), 129.0 (CH), 128.7 (CH), 126.9 (CH), 124.6 (C), 123.8 (CH), 122.7 (C), 116.8 (CH), 113.8 (C), 112.4 (CH), 84.7($CH_2$), 56.8 (OMe), 44.8 ($CH_2$), 37.5 (CH), 29.1 ($CH_2$), 24.2 ($CH_2$); MS (FAB) ($m/z$) 402 [(M + 2 + H)$^+$, 91], 400 [(M + H)$^+$, 91]; HRMS (FAB) calcd for $C_{20}H_{19}BrNO_3$ [(M + H)$^+$] 400.0548, found 400.0546. Anal. Calcd for $C_{20}H_{18}BrNO_3$: C, 60.01; H, 4.53; N, 3.50. Found: C, 59.62; H, 4.73; N, 3.42.

**Radical Cyclization of 7b: Obtention of (3a*R**,12b*R**)-7-Methoxy-2,3,3a,4,12b,13-hexahydro-1*H*-pyrrolo[1,2-*a*]xantheno[1,9-*de*]azepin-1-one (*trans*-2a) and (3a*S**,12b*R**)-7-Methoxy-2,3,3a,4,12b,13-hexahydro-1*H*-pyrrolo[1,2-*a*]xantheno[1,9-*de*]azepin-1-one (*cis*-2a).** To a solution of **7b** (500 mg, 1.25 mmol) in 118 mL of dry degassed $C_6H_6$, refluxing under argon, was added a solution of $n$-$Bu_3SnH$ (677 $\mu$L, 2.5 mmol) and AIBN (100 mg, 20% by weight) in $C_6H_6$ (39 mL) over 30 min. Once addition had finished, refluxing was kept up for a further 2 h. The solvent was evaporated, and the residue was dissolved in acetonitrile. This solution was washed with hexane, concentrated, and chromatographed ($SiO_2$, 1:1 EtOAc/hexane) to afford ***trans*-2a** (less polar product, $R_f$ 0.20, 210 mg, 53%, recrystallized from $CH_2Cl_2$/hexane) and ***cis*-2a** (more polar product, $R_f$ 0.17, 51 mg, 12%, recrystallized from $CH_2Cl_2$/hexane):

***trans*-2a:** mp 195 °C; IR (KBr) 1683 (CO) cm$^{-1}$; $^1$H NMR $\delta$ 7.46 (d, $J$ = 7.4 Hz, 1H), 7.22−6.87 (m, 3H), 6.83 (d, $J$ = 8.2 Hz, 1H), 6.76 (d, $J$ = 8.2 Hz, 1H), 4.54 (d, $J$ = 13.6 Hz, 1H), 4.20 (d, $J$ = 10.1 Hz, 1H), 3.93 (s, 3H, OMe), 3.64−3.50 (m, 1H), 3.02 (dd, $J$ = 14.2, 11.1 Hz, 1H), 2.94 (dd, $J$ = 13.6, 10.1 Hz, 1H), 2.78 (d, $J$ = 14.2 Hz, 1H), 2.62−2.26 (m, 3H), 1.75−1.70 (m, 1H); $^{13}$C NMR/ DEPT $\delta$ 174.4 (CO), 150.1 (C), 146.9 (C), 139.7 (C), 130.7(C), 130.1 (CH), 128.4 (CH), 123.7 (CH), 126.6 (C), 123.2 (CH), 120.2 (C), 116.5 (CH), 110.1 (CH), 59.2 (CH), 56.2 (OMe), 52.0 ($CH_2$), 43.8 ($CH_2$), 37.9 (CH), 30.0 ($CH_2$), 25.4 ($CH_2$); MS (EI) ($m/z$) 321 (M$^+$, 100), 306 (51), 290 (25), 209 (31); HRMS (EI) calcd for $C_{20}H_{19}NO_3$ 321.1365, found 321.1358. Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.41; H, 5.64; N, 4.18.

***cis*-2a:** mp 188 °C; IR (NaCl) 1680 cm$^{-1}$; $^1$H NMR $\delta$ 7.24−7.12 (m, 3H), 7.04 (dt, $J$ = 8.0, 2.0 Hz, 1H), 6.80 (d, $J$ = 8.4 Hz, 1H), 6.76 (d, $J$ = 8.4 Hz, 1H), 4.50 (dd, $J$ = 10.6, 8.3 Hz, 1H), 4.01 (dd, $J$ = 13.6, 10.6 Hz, 1H), 3.99 (t, $J$ = 7.2 Hz, 1H), 3.89 (s, 3H, OMe), 3.37 (dd, $J$ = 13.6, 8.3 Hz, 1H), 3.35 (dd, $J$ = 14.6, 7.2 Hz, 1H), 2.53 (d, $J$ = 14.6 Hz, 1H), 2.22−2.03 (m, 3H), 1.87−1.74 (m, 1H); $^{13}$C NMR/ DEPT $\delta$ 175.8 (CO), 149.6 (C), 147.0 (C), 140.3 (C), 128.3 (CH), 128.0 (CH), 126.9 (C), 123.3 (CH), 122.9 (CH), 121.4 (C), 120.1 (CH), 117.1 (CH), 110.2 (CH), 56.1 (OMe), 55.6 (CH), 47.8 ($CH_2$), 37.0 ($CH_2$), 33.2 (CH), 30.3 ($CH_2$), 25.4 ($CH_2$); MS (EI) ($m/z$) 321 (M$^+$, 100), 306 (56), 290 (31), 209 (56); HRMS (EI) calcd for $C_{20}H_{19}NO_3$ 321.1365, found 321.1356.

**Heck Reaction of 7b: Obtention of (3a*S**,11b*R**)-6-methoxy-3a-methyl-3,3a,11b,12-tetrahydrochromeno[4,3,2-*de*]pyrrolo[2,1-*a*]isoquinolin-1(2*H*)-one (9).** A mixture of **7b** (78 mg, 0.195 mmol), palladium acetate (9 mg, 0.04 mmol), tri-*o*-tolylphosphine (12 mg, 0.039 mg), sodium formate (14 mg, 0.199 mmol), triethylamine (0.2 mL, 1.43 mmol), and acetonitrile (3 mL) was heated at 80 °C for 18 h. The mixture was filtered through Celite, and the solvent was evaporated. The residue was chromatographed in alumina (1:1 EtOAc/hexane) to afford **9** (50 mg, 80%) which was recrystallized from $CH_2Cl_2$/hexane: mp 205 °C dec; IR (NaCl) 1682 cm$^{-1}$; $^1$H NMR $\delta$ 7.33−7.19 (m, 3H), 7.13−7.07 (m, 1H), 6.89 (d, $J$ = 8.4 Hz, 1H), 6.85 (d, $J$ = 8.4 Hz, 1H), 4.55 (dd, $J$ = 11.4, 7.4 Hz, 1H), 4.42 (dd, $J$ = 11.9, 7.4 Hz, 1H), 3.95 (s, 3H, OMe), 3.43 (t, $J$ = 11.6 Hz, 1H), 2.78−2.67 (m, 1H), 2.45−2.05 (m, 3H), 1.53 (s, 3H, Me); $^{13}$C NMR/ DEPT $\delta$ 173.7 (CO), 149.7 (C), 146.2(C), 139.3 (C), 135.5(C), 128.3 (CH), 126.4 (CH), 123.4 (CH), 120.0 (C), 117.1 (C), 116.7 (CH), 116.3 (CH), 110.6 (CH), 61.3 (C), 56.2 (OMe), 44.3 ($CH_2$), 34.6 ($CH_2$), 30.1 ($CH_2$), 28.5 (Me), 28.0 (CH); MS (EI) ($m/z$) 321 (M$^+$, 6), 306 [(M − Me), 100], 291 (7), 262 (4), 221 (5); HRMS (EI) calcd for $C_{20}H_{19}NO_3$ 321.1365, found 321.1375.

**Diethyl *N*-[(4-Methoxy-9*H*-xanthen-9-yl)methyl]glutamate (10a).** A mixture of **5a** (640 mg, 2.6 mmol), diethyl 2-bromopentanodioate (814 mg, 3.05 mmol), and $Na_2CO_3$ (1.36 g, 12.8 mmol) was heated at 105 °C under argon for 2.5 h. The mixture was partitioned between $CH_2Cl_2$ and water, the organic layer was washed with water, dried with $Na_2SO_4$, and filtered, and the solvent was evaporated. Purification by flash chromatography ($SiO_2$, 1:4 EtOAc/hexane) gave oil **10a** (782 mg, 69%) as a mixture of diastereoisomers: IR (NaCl) 3342 (NH), 1732 (CO) $cm^{-1}$; $^1H$ NMR $\delta$ 7.25−6.82 (m, 7H), 4.10 (q, $J = 7.1$ Hz, 2H), 4.07 (q, $J = 7.1$ Hz, 2H), 4.05−3.98 (m, 1H), 3.93 (s, 3H, OMe), 3.10−3.05 (m, 1H), 2.90 (dd, $J = 11.7$, 6.6 Hz, 1H), 2.66−2.60 (m, 1H), 2.31−2.25 (m, 2H), 1.89−1.72 (m, 2H), 1.45 (bs, 1H, NH), 1.24 (t, $J = 7.1$ Hz, 3H), 1.16 (t, $J = 7.1$ Hz, 3H); $^{13}C$ NMR/ DEPT $\delta$ 174.9 (CO), 174.8 (CO), 173.6 (CO × 2), 152.5 (C), 152.4 (C), 148.3 (C), 148.2 (C), 142.2 (C), 129.1 (CH), 129.0 (CH), 128.2 (CHx2), 125.1 (C), 125.0 (C), 123.9 (C), 123.7 (CH), 123.6 (CH), 123.2 (CH), 123.1 (CH), 121.0 (CH), 120.9 (CH), 117.1 (CH), 117.0 (CH), 110.8 (CH), 110.7 (CH), 61.2 (CH), 61.0 ($CH_2$), 60.7 ($CH_2$), 56.7 ($CH_2$), 56.6 (OMe), 56.5 (OMe), 40.7 (CH), 40.6 (CH), 30.9 ($CH_2$), 30.8 ($CH_2$), 28.3 ($CH_2$), 14.6 ($CH_3$), 14.5 ($CH_3$); MS (FAB) (*m*/*z*) 428 [(M + H)$^+$, 100]; HRMS (FAB) calcd for $C_{24}H_{30}NO_6$ [(M + H)$^+$] 428.2073, found 428.2075.

**Ethyl 1-[(4-Methoxy-9*H*-xanthen-9-yl)methyl]-5-oxoprolinate (11a).** Compound **10a** (600 mg, 1.40 mmol) was heated at 130 °C under argon for 3 days. Flash chromatography ($SiO_2$, 95:5 $CH_2Cl_2$/MeOH) gave oil **11a** (481 mg, 90%) as a mixture of diastereoisomers: IR (NaCl) 1739 (CO), 1698 (CO) $cm^{-1}$; $^1H$ NMR $\delta$ 7.35 (d, $J = 7.1$ Hz, 1H), 7.32−7.22 (m, 3H), 7.15−7.06 (m, 4H), 7.02 (t, $J = 8.2$ Hz, 2H), 6.94 (dd, $J = 7.7$, 1.5 Hz, 1H), 6.89 (dd, $J = 8.1$, 1.4 Hz, 1H), 6.86 (dd, $J = 8$, 1.5 Hz, 1H), 6.73 (dd, $J = 7.6$, 1.4 Hz, 1H), 4.37 (dd, $J = 9.2$, 5.5 Hz, 2H), 4.17−4.01 (m, 6H), 3.95 (s, 3H, OMe), 3.94 (s, 3H, OMe), 3.29 (dd, $J = 9.1$, 2.4 Hz, 1H), 3.22 (dd, $J = 9.1$, 2.4 Hz, 1H), 2.81 (dd, $J = 9.3$, 6.6 Hz, 1H), 2.76 (dd, $J = 9.3$, 6.6 Hz, 1H), 2.44−1.80 (m, 8H), 1.17 (t, $J = 7.1$ Hz, 3H), 1.16 (t, $J = 7.1$, 3H); $^{13}C$ NMR/ DEPT $\delta$ 175.9 (CO), 172.1 (CO), 172.0 (CO), 152.4 (C), 152.3 (C), 148.4 (C), 148.3 (C), 142.1 (C), 141.9 (C), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 124.6 (C), 124.2 (CH), 124.1 (C), 123.8 (CH), 123.6 (CH), 123.4 (C), 123.2 (CH), 123.0 (C), 120.9 (CH), 120.7 (CH), 117.2 (CH), 111.1 (CH), 111.0 (CH), 61.9 ($CH_2$), 61.8 (CH), 61.7 (CH), 56.5 (OMe), 50.8 ($CH_2$), 50.5 ($CH_2$), 38.1 (CH), 38.0 (CH), 29.6 ($CH_2$), 23.7 ($CH_2$), 23.6 ($CH_2$), 14.4 ($CH_3$); MS (FAB) (*m*/*z*) 382 [(M + H)$^+$, 100]; HRMS (FAB) calcd for $C_{22}H_{24}NO_5$ [(M + H)$^+$] 382.1654, found 382.1652.

**5-(Hydroxymethyl)-1-[(4-methoxy-9*H*-xanthen-9-yl)methyl]-pyrrolidin-2-one (15a).** LiCl (66 mg, 1.52 mmol) and $NaBH_4$ (59 mg, 1.52 mmol) were added to a solution of ester **11a** (290 mg, 0.76 mmol) in THF (6 mL). The mixture was cooled to 0 °C, and EtOH (12 mL) was added dropwise. After 12 h at rt, AcOH was added until neutral pH, and the solvents were removed under reduced pressure. The residue was partitioned between $CH_2Cl_2$ and water, and the organic layer was washed with brine, dried with $Na_2SO_4$, filtered, and concentrated to afford **15a** (239 mg, 93%) as a foam: IR (KBr) 3378 (OH), 1667 (CO) $cm^{-1}$; $^1H$ NMR $\delta$ 7.33−6.75 (m, 13H), 6.76 (dd, $J = 7.6$, 1.3 Hz, 1H), 4.49−4.43 (m, 2H), 3.94 (s, 6H, OMe), 3.70−3.62 (m, 2H), 3.43 (dd, $J = 12.0$, 5.0 Hz, 1H), 3.42 (t, $J = 6.0$ Hz, 1H), 3.23 (t, $J = 7.6$ Hz, 1H), 3.22 (dd, $J = 8.6$, 4.5 Hz, 1H), 3.02 (dd, $J = 8.8$, 6.7 Hz, 1H), 2.97 (dd, $J = 8.8$, 6.7 Hz, 1H), 2.85−2.75 (m, 2H), 2.41−1.82 (m, 10H); $^{13}C$ NMR/ DEPT $\delta$ 176.2 (CO × 2), 151.6 (C × 2), 147.5 (C), 147.4 (C), 141.2 (C), 141.1 (C), 128.5 (CH), 128.3 (CH), 127.8 (CH × 2), 123.9 (C × 2), 123.6 (C × 2), 123.2 (CH), 122.9 (CH × 2), 122.5 (CH), 120.2 (CH), 120.0 (CH), 116.3 (CH), 116.2 (CH), 110.3 (CH × 2), 61.6 ($CH_2$ × 2), 60.7 (CH × 2), 56.6 (OMe × 2), 48.7 ($CH_2$), 48.5 ($CH_2$), 36.8 (CH × 2), 30.0 ($CH_2$ × 2), 21.0 ($CH_2$ × 2); MS (CI) (*m*/*z*) 340 [(M + H)$^+$,100], 211 (12), 168 (10); HRMS (CI) calcd for $C_{20}H_{22}NO_4$ 340.1549, found 340.1540.

**1-[(4-Methoxy-9*H*-xanthen-9-yl)methyl]-5-oxopyrrolidine-2-carbaldehyde (16a).** Dess−Martin periodinane (210 mg, 0.49 mmol) and *t*-BuOH (47 $\mu$L, 0.49 mmol) were added to a solution of alcohol **15a** (168 mg, 0.49 mmol) in dry acetonitrile (15 mL), and the mixture was stirred at rt for 12 h. The solvent was evaporated, and the residue was dissolved in $CH_2Cl_2$ and treated with a mixture $Na_2S_2O_3$/$NaHCO_3$/$H_2O$ (5.25 g/0.75 g/12 mL). After the mixture was stirred for 20 min, the organic phase was washed with water, dried with $Na_2SO_4$, filtered, and concentrated to afford **16a** (150 mg, 90%) as an oil: IR (KBr) 1728 (CHO), 1684 (CO) $cm^{-1}$; $^1H$ NMR $\delta$ 9.17 (d, $J = 4.7$ Hz, 1H), 9.15 (d, $J = 4.7$ Hz, 1H), 7.31−6.75 (m, 13H), 6.76 (dd, $J = 7.6$, 1.3 Hz, 1H), 4.42−4.37 (m, 2H), 4.05−3.96 (m, 2H), 3.93 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.90−3.85 (m, 2H), 3.29 (ddd, $J = 9.5$, 3.4, 1.3 Hz, 1H), 3.25 (ddd, $J = 9.4$, 3.4, 1.3 Hz, 1H), 2.95−1.84 (m, 8H); $^{13}C$ NMR/ DEPT $\delta$ 198.1 (CHO), 197.0 (CHO), 175.3 (C), 175.2 (C), 152.0 (C), 151.9 (C), 147.9 (C), 147.8 (C), 141.5 (C), 141.4 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 123.9 (CH), 123.6 (C), 123.5 (C), 123.3 (CH), 123.2 (CH), 122.8 (C), 122.7 (C), 122.4 (CH), 120.3 (CH), 120.1 (CH), 116.7 (CH × 2), 110.7 (CH × 2), 66.9 (CH), 66.8 (CH), 56.0 (OMe), 55.9 (OMe), 50.4 ($CH_2$), 50.2 ($CH_2$), 37.6 (CH), 37.5 (CH), 28.8 ($CH_2$x2), 19.4 ($CH_2$), 19.3 ($CH_2$); MS (CI) (*m*/*z*) 338 [(M + H)$^+$, 3], 211 (22), 196 (15), 168 (40), 98 (100); HRMS (CI) calcd for $C_{20}H_{20}NO_4$ 338.1392, found 338.1396.

**Cyclization of Aldehydes 16a−c: 7-Methoxy-2,3,12b,13-tetrahydro-1*H*-pyrrolo[1,2-*a*]xantheno[1,9-*de*]azepin-1-one (8a).** A mixture of aldehyde (**16a**) (200 mg, 0.59 mmol), AcOH (4 mL), and concd HCl (1.4 mL) was heated at 80 °C for 30 min, diluted with water, and extracted with $CH_2Cl_2$. The organic layer was washed with 1 M NaOH and then with water, dried with $Na_2SO_4$, filtered, and concentrated. Flash chromatography ($SiO_2$, 99:1 $CH_2Cl_2$/MeOH) gave **8a** (124 mg, 65%), which was recrystallized from $CH_2Cl_2$/hexane: mp 175 °C; IR (KBr) 1719 (CO), 1658 (CO) $cm^{-1}$; $^1H$ NMR $\delta$ 7.40 (d, $J = 7.7$ Hz, 1H), 7.22 (dd, $J = 8.2$, 1.4 Hz, 1H), 7.15−7-06 (m, 2H), 6.81 (d, $J = 8.5$ Hz, 1H), 6.76 (d, $J = 8.5$ Hz, 1H), 5.60 (s, 1H), 4.82 (d, $J = 13.5$ Hz, 1H), 4.12 (d, $J = 8.5$ Hz, 1H), 3.92 (s, 3H, OMe), 3.38 (dd, $J = 13.5$, 8.5 Hz, 1H), 2.94−2.74 (m, 2H), 2.66−2.60 (m, 2H); $^{13}C$ NMR/ DEPT $\delta$ 175.3 (CO), 150.6 (C), 146.2 (C), 139.6 (C), 138.9 (C), 130.0 (CH), 129.0 (CH), 128.1 (C), 123.9 (CH), 123.0 (CH), 121.5 (C), 120.2 (C), 117.0 (CH), 111.1 (CH), 103.0 (CH), 56.7 (OMe), 53.3 ($CH_2$), 37.6 (CH), 29.7 ($CH_2$), 24.9 ($CH_2$); MS (EI) (*m*/*z*) 319 (M$^+$, 85), 304 (53), 288 (39), 163 (60), 42 (100); HRMS (EI) calcd for $C_{20}H_{17}NO_3$ 319.1208, found 319.1208. Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.02; H, 5.07; N, 4.23.

**8-Methoxy-3,4,13b,14-tetrahydropyrido[1,2-*a*]xantheno[1,9-*de*]azepin-1(2*H*)-one (8b).** Aldehyde **16b** (600 mg, 1.7 mmol), concd HCl (2.2 mL), and AcOH (6 mL) were heated at 75 °C for 45 min. After workup as described for **8a**, the residue (464 mg) was taken into ether/hexane and **8b** (285 mg, 50%) was filtered out: mp 165 °C; IR (KBr) 1662 (CO) $cm^{-1}$; $^1H$ NMR $\delta$ 7.75 (d, $J = 8.0$ Hz, 1H), 7.24−7.07 (m, 3H), 6.85 (d, $J= 8.5$ Hz, 1H), 6.78 (d, $J = 8.5$ Hz, 1H), 5.66 (s, 1H), 5.53 (d, $J = 13.5$ Hz, 1H), 3.97−3.93 (m, 1H), 3.93 (s, 3H, OMe), 3.05 (dd, $J = 13.5$, 7.1 Hz, 1H), 2.72−2.64 (m, 4H), 1.99−1.86 (m 2H); $^{13}C$ NMR/ DEPT $\delta$ 168.6 (CO), 149.8 (C), 145.9 (C), 138.7 (C), 135.0 (C), 129.6 (CH), 128.2 (CH), 127.8 (C), 124.4 (CH), 123.4 (CH), 122.0 (C), 120.3 (C), 116.2 (CH), 110.0 (CH), 108.8 (CH), 56.1 (OMe), 52.7 ($CH_2$), 39.1 (CH), 32.7 ($CH_2$), 32.6 ($CH_2$), 20.3 ($CH_2$); MS (EI) (*m*/*z*) 333 (M$^+$, 100), 318 (41), 302 (19); HRMS (EI) calcd for $C_{21}H_{19}NO_3$ 333.1365, found 333.1372.

**7-Methoxy-1,2,3,12b-tetrahydro-13*H*-pyrrolo[1,2-*a*]xantheno-[1,9-*de*]azepin-13-one (8c).** Aldehyde **16c** (380 mg, 1.12 mmol) was dissolved in AcOH (4 mL), concd HCl (1.4 mL) was added, and the mixture was heated at 70 °C for 20 min. After workup as in the preparation of **8a**, the residue was purified by column chromatography ($Al_2O_3$, $CH_2Cl_2$) giving **8c** (167 mg, 47%): mp 210 °C; IR (KBr) 1662 (CO); $^1H$ NMR $\delta$ 7.68−6.97 (m, 4H), 6.92 (d, $J = 8.5$ Hz, 1H), 6.88 (d, $J = 8.5$ Hz, 1H), 6.29 (s, 1H), 4.45

(s, 1H), 3.94 (s, 3H, OMe), 3.99−3.88 (m, 1H), 3.69−3.60 (m, 1H), 3.02−2.89 (m, 1H), 2.71 (ddd, $J$ = 14.9, 7.6, 3.5 Hz, 1H), 2.04−1.96 (m, 2H); $^{13}$C NMR/ DEPT $\delta$ 166.7 (CO), 150.8 (C), 147.0 (C), 139.5 (C), 139.2 (C), 130.5 (CH), 128.5 (CH), 127.7 (C), 122.7 (CH), 120.1 (CH), 116.9 (C), 116.5 (CH), 115.0 (C), 111.2 (CH), 108.0 (CH), 56.4 (OMe), 48.4 ($CH_2$), 43.6 (CH), 32.7 ($CH_2$), 20.8 ($CH_2$); MS (EI) ($m/z$) 319 (M$^+$, 100), 290 (67), 288 (88), 211 (38); HRMS (EI) calcd for $C_{20}H_{17}NO_3$ 319.1208, found 319.1224.

**Hydrogenation of 8a−c: (3a*S**,12b*R**)-7-Methoxy-2,3,3a,4,12b,13-hexahydro-1*H*-pyrrolo[1,2-*a*]xantheno[1,9-*de*]azepin-1-one (*cis*-2a).** Alkene **8a** (20 mg, 0.06 mmol) and 10% Pd/C (10 mg) were stirred in THF (8 mL) under 1 atm of $H_2$ for 12 h. Filtration through Celite and evaporation of the solvent in vacuo afforded ***cis*-2a** (18 mg, 90%).

**(4a*S**,13b*R**)-8-Methoxy-3,4,4a,5,13b,14-hexahydropyrido[1,2-*a*]xantheno[1,9-*de*]azepin-1(2*H*)-one (*cis*-3a).** Alkene **8b** (52 mg, 0.156 mmol), 10% Pd/C (20 mg), and THF (8 mL) were used as described for the hydrogenation of **8a**. After workup, the residue was purified by flash chromatography ($SiO_2$, 99:1 $CH_2Cl_2$/MeOH) giving ***cis*-3a** (27 mg, 52%) which was recrystallized from $CH_2Cl_2$/hexane: mp 239 °C; IR (KBr) 1623 (CO) cm$^{-1}$; $^{1}$H NMR $\delta$ 7.25−7-15 (m, 3H), 7.07−7.04 (m, 1H), 6.77 (d, $J$ = 8.2 Hz, 1H), 6.74 (d, $J$ = 8.2 Hz, 1H), 4.55 (dd, $J$ = 13.0, 9.8 Hz, 1H), 4.40 (t, $J$ = 8.5 Hz, 1H), 4.04−3.96 (m, 1H), 3.89 (s, 3H, OMe), 3.30 (dd, $J$ = 15.0, 8.4 Hz, 1H), 3.29 (dd, $J$ = 13.0, 7.3 Hz, 1H), 2.66 (dd, $J$ = 15.0, 3.5 Hz, 1H), 2.27−1.72 (m, 6H); $^{13}$C NMR/ DEPT $\delta$ 170.1 (CO), 149.8 (C), 146.7 (C), 140.1 (C), 128.9 (C), 128.1 (CHx2), 123.1 (CH), 122.5 (CH), 121.4 (C), 119.8 (C), 116.9 (CH), 110.2 (CH), 56.0 (OMe), 53.5 (CH), 50.9 ($CH_2$), 39.0 ($CH_2$), 34.1 (CH), 31.8 ($CH_2$), 30.1 ($CH_2$), 17.3 ($CH_2$); MS (EI) ($m/z$): 335 (M$^+$, 61), 249 (100), 225 (70), 218 (40); HRMS (EI) calcd for $C_{21}H_{21}NO_3$ 335.1521, found 335.1517.

**(3a*S**,12b*R**)-7-Methoxy-1,2,3,3a,4,12b-hexahydro-13*H*-pyrrolo[1,2-*a*]xantheno[1,9-*de*]azepin-13-one (*cis*-2d).** Alkene **8c** (94 mg, 0.29 mmol), 10% Pd/C (20 mg), and THF (25 mL) were used as described in the hydrogenation of **8a**. The residue was taken into hexane, and ***cis*-2d** (93 mg, 98%) was filtered out: mp 210 °C dec; IR (KBr) 1653 (CO) cm$^{-1}$; $^{1}$H NMR $\delta$ 7.78−6.85 (m, 4H), 6.79 (d, $J$ = 8.3 Hz, 1H), 6.76 (d, $J$ = 8.3 Hz, 1H), 5.33 (s, 1H), 4.44−4.33 (m, 1H), 3.90 (s, 3H, OMe), 3.54−3.49 (m, 2H), 3.40 (dd, $J$ = 16.2, 6.6 Hz, 1H), 2.90 (dd, $J$ = 16.2, 7.4 Hz, 1H), 2.25−2.19 (m, 1H), 1.92−1.67 (m, 3H); $^{13}$C NMR/ DEPT $\delta$ 169.9 (CO), 150.4 (C), 146.6 (C), 140.0 (C), 130.6 (CH), 128.6 (CH), 126.9 (C), 123.6 (CH), 122.8 (CH), 117.8 (C), 117.0 (C), 116.6 (CH), 110.9 (CH), 56.3 (OMe), 55.9 (CH), 46.5 ($CH_2$), 41.7 (CH), 36.8 ($CH_2$), 33.6 ($CH_2$), 22.1 ($CH_2$); MS (EI) ($m/z$) 321 (M$^+$, 100), 290 (17), 249 (29), 209 (85); HRMS (EI) calcd for $C_{20}H_{19}NO_3$ 321.1365, found 321.1359.

**1-[(1-Bromo-4-methoxy-9*H*-xanthen-9-yl)methyl]-1*H*-pyrrole (17).** 2,5-Dimethoxytetrahydrofuran (407 $\mu$L, 2.86 mmol) was added to a suspension of *C*-(1-bromo-4-methoxy-9*H*-xanthen-9-yl)methylamine (**5b**) (476 mg, 1.48 mmol) in a mixture of water (4.8 mL) and AcOH (2.4 mL). After the mixture was heated at 50 °C for 2 h, the solvents were removed under reduced pressure and the residue was partitioned between $CH_2Cl_2$ and water. The organic layer was washed with water, dried with $Na_2SO_4$, filtered, and concentrated. Purification by flash chromatography ($SiO_2$, 1:1 $CH_2Cl_2$/hexane) gave **17** (487 mg, 89%): mp 110 °C; IR (KBr) 1571, 1493, 1473 cm$^{-1}$; $^{1}$H NMR $\delta$ 7.25 (d, $J$ = 8.8 hz, 1H), 7.25−7.14 (m, 2H), 6.91 (ddd, $J$ = 7.5, 6.9, 1.7 Hz, 1H), 6.72 (d, $J$ = 8.8 Hz, 1H), 6.50 (dd, $J$ = 7.5, 1.1 Hz, 1H), 6.29 (t, $J$ = 2.1 Hz, 2H), 6.04 (t, $J$ = 2.1 Hz, 2H), 4.48 (dd, $J$ = 9.0, 3.6 Hz, 1H), 4.22 (dd, $J$ = 13.6, 3.6 Hz, 1H), 3.86 (s, 3H, OMe), 3.78 (dd, $J$ = 13.6, 9.0 Hz, 1H); $^{13}$C NMR/ DEPT $\delta$ 151.2 (C), 147.6 (C), 143.0 (C), 128.8 (CH), 128.3 (CH), 126.3 (CH), 123.5 (CH), 122.3 (C), 121.6 (C), 120.9 (CH × 2), 116.1 (CH), 113.5 (C), 111.9 (CH), 108.0 (CH × 2), 56.1 (OMe), 55.1 ($CH_2$), 42.5 (CH); MS (CI) ($m/z$) 372 [(M + 2 + H)$^+$, 19], 370 [(M + H)$^+$, 22], 290 (11), 139 (9), 80 (100); HRMS (CI) calcd for $C_{19}H_{17}BrNO_2$ [(M + H)$^+$] 370.0443, found 370.0436.

**4-Methoxy-9-(1*H*-pyrrol-1-ylmethyl)-9*H*-xanthene-1-carboxylic Acid (18).** A solution of **17** (150 mg, 0.4 mmol) in THF (3 mL) was cooled to −78 °C, and 2.5 M *n*-BuLi (162 $\mu$L, 0.4 mmol) in hexane was added. After 5 min, $CO_2$ was bubbled through the solution, and the stirring was continued for an additional 30 min at rt. AcOH (0.1 mL) was added, and the solvents were removed under reduced pressure. The residue was loaded onto silica and purified by flash chromatography (99:1 $CH_2Cl_2$/MeOH) giving **18** (108 mg, 80%) which was recrystallized from $CH_2Cl_2$/hexane: mp 253 °C; IR (KBr) 3433 (OH), 1673 (CO); $^{1}$H NMR $\delta$ 8.06 (d, $J$ = 8.8 Hz, 1H), 7.33−7.18 (m, 2H), 6.97 (d, $J$ = 8.8 Hz, 1H), 6.98−6.91 (m, 1H), 6.57 (d, $J$ = 6.6 Hz, 1H), 6.37 (t, $J$ = 1.9 Hz, 2H), 6.05 (t, $J$ = 1.9 Hz, 2H), 5.41 (dd, $J$ = 9.0, 4.1 Hz, 1H), 4.32 (dd, $J$ = 13.4, 4.1 Hz, 1H), 4.03 (s, 3H, OMe), 3.82 (dd, $J$ = 13.4, 9.0 Hz, 1H); $^{13}$C NMR/ DEPT (DMSO-$d_6$) $\delta$ 168.5 (CO), 152.0 (C), 151.9 (C), 142.7 (C), 129.6 (CH), 129.1 (CH), 128.4 (CH), 125.9 (C), 124.2 (CH), 123.4 (C), 121.6 (CH in hexane2), 121.2 (C), 116.5 (CH), 111.0 (CH), 108.4 (CH in hexane2), 56.9 ($CH_2$), 56.8 (OMe), 39.8 (CH); MS (EI) ($m/z$) 335 (M$^+$, 4), 255 (100), 195 (15); HRMS (EI) calcd for $C_{20}H_{17}NO_4$ 335.1158, found 335.1155.

**7-Methoxy-12b,13-dihydro-4*H*-pyrrolo[1,2-*a*]xantheno[1,9-*de*]azepin-4-one (19).** A solution of acid **18** (93 mg, 0.27 mmol), polyphosphate ester (PPE)[25] (1 g), and $CHCl_3$ (12 mL) was refluxed for 10 min under argon. The mixture was partitioned between $CHCl_3$ and water, and the organic layer was washed with water, dried with $Na_2SO_4$, filtered, and concentrated. Purification by flash chromatography ($SiO_2$, $CH_2Cl_2$) gave **19** (79 mg, 90%): mp 120 °C; IR (KBr) 1627 (CO); $^{1}$H NMR $\delta$ 7.81 (d, $J$ = 8.7 Hz, 1H), 7.40 (dd, $J$ = 4.0, 1.8 Hz, 1H), 7.34 (d, $J$ = 7.6 Hz, 1H), 7.30 (dd, $J$ = 8.0, 7.4 Hz, 1H), 7.21 (d, $J$ = 8.0 Hz, 1H), 7.14 (t, $J$ = 7.4 Hz, 1H), 7.00 (d, $J$ = 8.7 Hz, 1H), 6.92 (t, $J$ = 2.0 Hz, 1H), 6.29 (dd, $J$ = 4.0, 2.3 Hz, 1H), 4.85 (dd, $J$ = 10.1, 1.1 Hz, 1H), 4.52 (dd, $J$ = 13.4, 10.1 Hz, 1H), 4.44 (dd, $J$ = 13.4, 1.1 Hz, 1H), 4.01 (s, 3H, OMe); $^{13}$C NMR/ DEPT $\delta$ 180.1 (CO), 150.9 (C), 149.8 (C), 137.6 (C), 133.1 (C), 130.1 (C), 129.1 (CH), 129.0 (CH), 128.4 (CH), 126.5 (CH), 123.8 (CH), 120.9 (C), 120.7 (CH), 118.7 (C), 116.8 (CH), 110.4 (CH), 109.9 (CH), 59.8 ($CH_2$), 56.1 (OMe), 37.0 (CH); MS (EI) ($m/z$) 317 (M$^+$, 69), 302 (10), 224 (85), 209 (100); HRMS (EI) calcd for $C_{20}H_{15}NO_3$ 317.1052, found 317.1046.

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**Supporting Information Available:** Most significant $^{13}$C and $^{1}$H NMR signals and NOE experiments for stereoisomers ***trans*-2a** and ***cis*-2a** (Table 1). Experimental procedures and characterization data for compounds **4b**,**c**, **5b**,**c**, **6c**, **7c**, **10b**, **11b**, **12a**, **13**, **14**, **11c**,**d**, **12c**, **15b**−**d**, **16b**−**d**. Copies of the $^{1}$H NMR and $^{13}$C NMR spectra for all new compounds **2a**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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