Tetrahedron Letters 49 (2008) 7174–7177

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Enantiospecific synthesis of 5-phenylpyrrolo[2,1-*c*][1,4]benzodiazepines

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ARTICLE INFO

Article history:
Received 27 May 2008
Revised 26 September 2008
Accepted 30 September 2008
Available online 2 October 2008

Dedicated to Professor Luis Castedo on the occasion of his 70th birthday

Keywords:
Pyrrolobenzodiazepine
Xanthene
Proline
Benzodiazepinone
Cyclodehydration

ABSTRACT

Enantiomerically pure 5-phenylpyrrolo[2,1-*c*][1,4]benzodiazepines were synthesized starting from 2-aminobenzophenones and 2-amino-4-methoxyxanthone, using L-proline as a chiral building block.

The 5-aryl-1,4-benzodiazepin-2-ones constitute an important class of privileged templates as they are able to provide ligands for diverse receptors such as the cholecystokinin receptor (CCK) and several central nervous system (CNS) receptors.[1] Besides the well-known clinically effective psychoactive drugs such as diazepam,[2] more than 10,000 benzodiazepines have been found to have pharmacological properties ranging from inhibition of the proliferation of tumor cells,[3] to antiviral[4] and analgesic[5] activities, to the blocking of sodium channel in the treatment of neuropathic pain.[6]

Pyrrolo[2,1-*c*][1,4]benzodiazepin-11-ones exhibit different biological properties.[7] They are useful for treatment of anxiety in warm-blooded animals,[8] and as a new class of anti-ischemic agents.[9] Their N_{10}–C_{11} imino derivatives (PBDs), which can be obtained from them chemically,[10] are gene-specific antitumor agents capable of binding to specific DNA sequences, forming aminal bonds by nucleophilic attack of the NH_2 of a guanine at their electrophilic C_{11} position.[11]

In view of the biological relevance of the above molecular families, we became interested in the synthesis of hybrids combining the 5-aryl- and pyrrolo-benzodiazepinone frameworks, such as unknown compounds 5-phenylpyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (**1a**) and the chromeno-fused derivative **2**, a rigid analogue in which the phenyl ring is conformationally frozen by the ether bridge (Fig. 1). A search of the literature showed only two previous reports of this structural motif, both concerning 3,11-diones in which the pyrrolidinone ring was constructed by intramolecular N-acylation of a 5-phenyl-1,4-benzodiazepin-2-one with a propanoate substituent at position 3.[12] Furthermore, only two other groups of tricyclic 5-aryl-3,4-fused [1,4]benzodiazepines have been described in the literature, the imidazo[5,1-*c*][13] and imidazo-[2,1-*c*][14] derivatives.

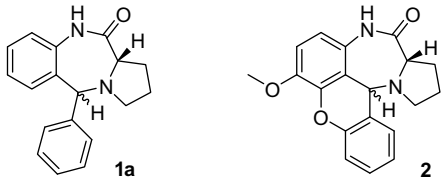

Figure 1. 5-Phenylpyrrolo[2,1-*c*][1,4]benzodiazepin-11-ones.

For the synthesis of **1a**, we started from 2-aminobenzophenone **3a**. This was condensed with L-Boc-Pro in the presence of isobutyl chloroformate[15] to provide amide **4a**, which was subsequently deprotected with TFA to afford **5a**, both steps proceeding in quantitative yield (Scheme 1). Reduction of the benzophenone carbonyl group with $NaBH_4$ in EtOH at rt gave a 99% yield of benzhydrol **6a** as a 10:3 mixture of stereoisomers, as evidenced by ^1H NMR.

All attempts to construct the N_4–C_5 bond of the required diazepinone ring by acidic cyclodehydration failed. Treatment of the diastereomeric mixture **6a** in acetic acid at rt for 48 h had no effect; heating this solution under reflux for 2 h led to extensive decomposition of the starting amide; and heating at 60 °C for

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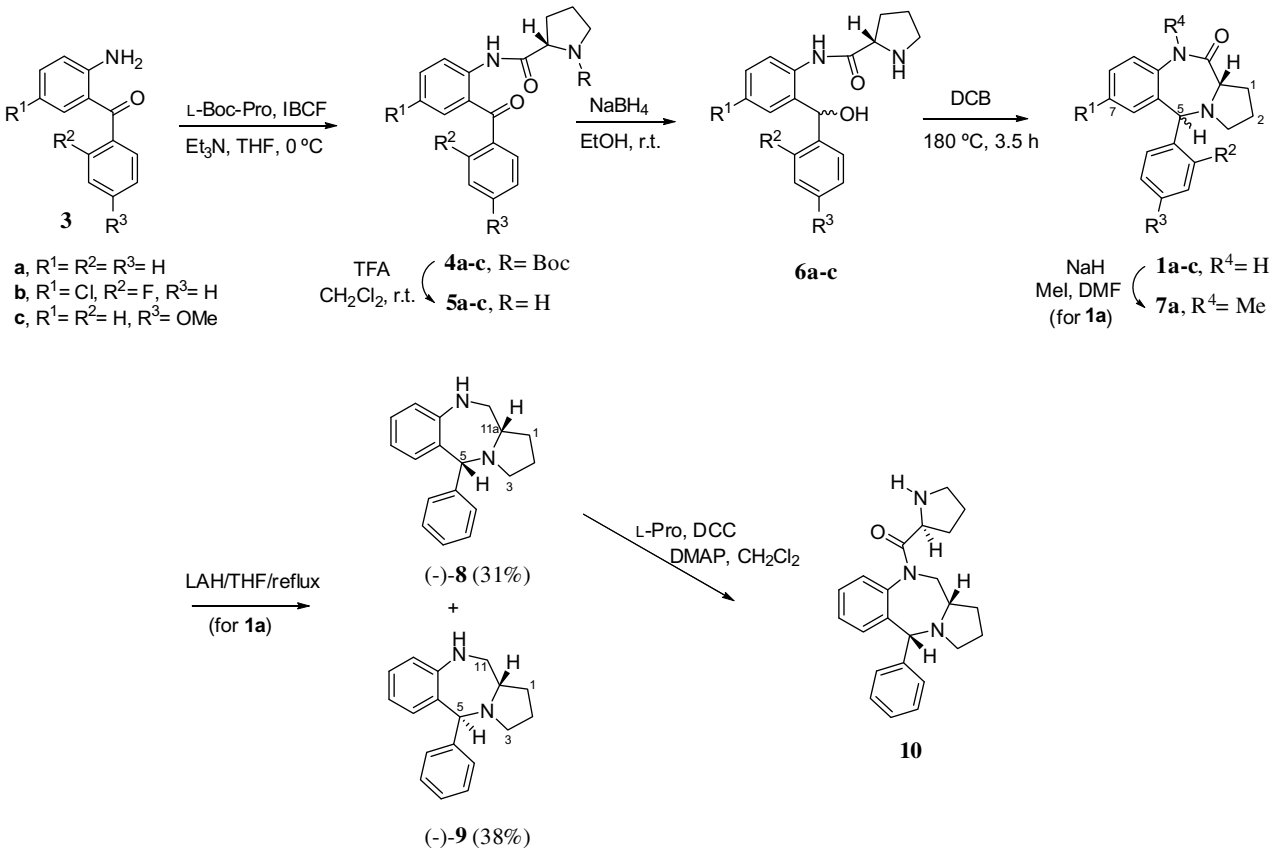
doi:10.1016/j.tetlet.2008.09.168



Scheme 1. Synthesis of *cis* and *trans* pyrrolo[2,1-*c*][1,4]benzodiazepines (−)-**8** and (−)-**9**.

24 h afforded (2-acetamidophenyl)(phenyl)methyl acetate as the main product, indicating cleavage of the amide bond of **6a** and subsequent N,O-diacetylation of the resulting (2-aminophenyl)(phenyl)methanol in the acetic acid medium. The use of *p*-TsOH in toluene, whether in catalytic quantities or in large excess, likewise produced no reaction at rt and decomposition at temperatures over 60 °C. Stirring for 24 h at rt in methanol saturated with HCl gave a 58% yield of the methyl ether resulting from an intermolecular displacement of the hydroxyl of **6a** by the solvent; while treatment with HCl–saturated diethyl ether in dichloromethane for 48 h at rt caused decomposition. Finally, heating at 100 °C in PPA for 1 h also led to decomposition of the starting material. Attempts to carry out the cyclodehydration using Lewis acid catalysts such as $TiCl_4$ or $BF_3{\cdot}OEt_2$ led to very complex reaction mixtures.

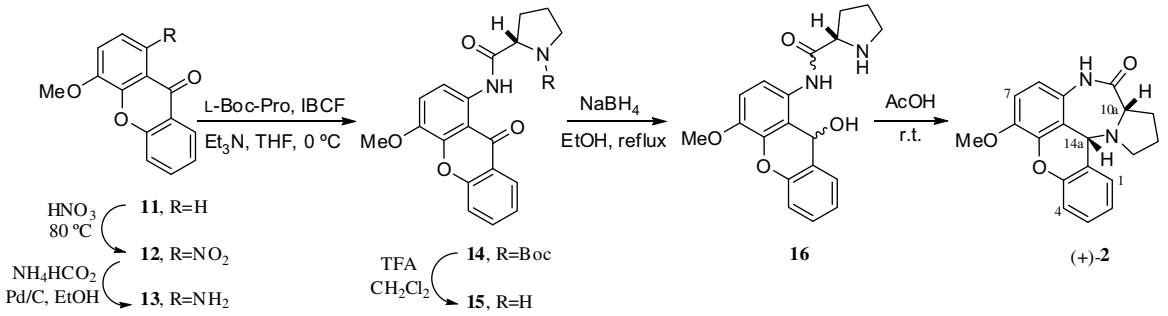
The reluctance of the system to undergo acidic cyclodehydration was attributed to **6a** existing mainly as its trans amide bond rotamer, in which the large distance between N_4 and C_5 (4.10 Å according to MM2 calculations) favors alternative reactions of an activated hydroxyl. We inferred that cyclodehydration under neutral conditions would require sufficient thermal energy to bring about rotation to the cis rotamer for the cyclization (Table 1). Nevertheless, prolonged heating of **6a** in refluxing toluene achieved no change, regardless of whether water was removed using a Dean–Stark trap (entry 1) or 4 Å molecular sieves (entry 2). Heating in dioxane in a sealed tube at 130 °C (entry 3) or in the ionic liquid Bmim[16] at 125 °C (entry 4) was also ineffective, and pre-adsorption on silica followed by heating in an oven at 170 °C led to extensive decomposition (entry 5). Finally, however, heating in dichlorobenzene at 180 °C in a sealed tube for 3.5 h (entry 6) led to an excellent 86% yield of the cyclodehydrated product **1a**, a yellow solid consisting of a 1:1 mixture of the cis and trans stereoisomers.[17] Chromatography failed to separate both this mixture and its

Table 1
Thermal cyclodehydration conditions tried for amide **6a**

Entry	Conditions	Solvent	Time	Temperature	Result
1	Dean–Stark	Toluene	24 h	Reflux	**6a**
2	4 Å MS	Toluene	24 h	Reflux	**6a**
3	4 Å MS	Dioxane	3 h	130 °C (sealed tube)	**6a**
4		Bmim	7 h	125 °C	**6a**
5	SiO_2 (preabsorbed)	—	5 min	170 °C	Decomposition
6		DCB	3.5 h	180 °C (sealed tube)	**1a** (1:1, 86%)

N-methylated derivative **7a** (obtained in 63% yield by treatment of **1a** with sodium hydride and methyl iodide in DMF), but LAH reduction of **1a** to the corresponding benzodiazepines allowed chromatographic separation of less polar and more polar isomers in 38% and 31% isolated yields, respectively.[18] Unambiguous identification of the relative stereochemistry of the minor isomer was possible on the basis of a 5% NOE on the intensity of the multiplet at 2.98–3.06 ppm (H_{11a}) upon irradiation of the singlet at 4.86 ppm (H_5), which clearly showed the cis arrangement of these protons (Scheme 1, **8**). By contrast, in the major isomer irradiation, of the singlet at 5.19 ppm (H_5) enhanced the multiplets at 2.92–3.00 ppm ($H_{11\alpha}$) and 2.82–2.87 ppm ($H_{3\alpha}$) by 2.3% and 2.2%, respectively, confirming the location of H_5 on the α-face trans to H_{11a} (Scheme 1, **9**).

The optical activity of (−)-**8** and (−)-**9** suggested preservation of the stereochemistry of C_{11a} (provided by the starting L-proline). Their enantiomeric purity initially seemed to have been confirmed when derivatization of (−)-**8** with L-proline afforded what appeared to be a diastereomerically pure amide, **10**. Furthermore,



Scheme 2. Synthesis of (14*aR*,10*aS*)-pyrrolo[1,2-*a*]xanthene[1,9-*e*,*f*][1,4]diazepin-10-one (**2**).

when this reaction was carried out on the unseparated mixture of (−)-**8** and (−)-**9**, H_5 singlets at 4.90 and 5.15 ppm in the ^{1}H NMR spectrum of the product appeared to show the presence of only two stereoisomers, amide **10** and the analogous derivative of (−)-**9**. However, since the spectrum of the derivatization product of *rac*-**8** (obtained starting from **3** and *rac*-Pro) did not clearly show amide **10** and the corresponding diastereoisomer, and since derivatization of *rac*-**9** afforded an analogous result, we sought and obtained additional evidence of enantiomeric purity. Successive additions of the chiral shift reagent Eu(hfc)$_3$ did not cause chemical shift changes in the ^{1}H NMR spectrum of (−)-**8**, but complexation of the carbonyl of **1a** by Eu(hfc)$_3$ shifted its H_5 signals at 4.69 and 5.02 ppm with no splitting, indicating an enantiomeric excess of more than 95%. By contrast, addition of 30% of Eu(hfc)$_3$ to *rac*-**1a**[19] clearly split its H_5 signals.

We thus accomplished a five-step synthesis of enantiomerically pure 5-phenylpyrrolo[2,1-*c*][1,4]benzodiazepine **1a** from 2-aminobenzophenone in 69% yield. Unfortunately, this protocol seems to be of limited scope, since attempts to cyclize the substituted benzhydrol **6b**,[20] whether thermally (DCB, 180 °C) or with Lewis acid catalysis ($BF_3{\cdot}OEt_2$, DCE, reflux), led to complex mixtures, probably due to the electron-withdrawing halogen substituents making the intermediate carbocation unstable. In the case of the methoxy-substituted benzhydrol **6c**,[21] heating at 180 °C in DCB led to decomposition, and reaction in acetic acid at rt afforded only in a very modest 18% yield of the cyclodehydration product.

We also synthesized the chromeno-fused pentacyclic derivative **2**, a rigid analogue of **1a** in which the conformation of the phenyl substituent is fixed by the ether bridge. We started from 4-methoxy-9*H*-xanthen-9-one (**11**), which is easily prepared in two steps from commercially available guayacol and *o*-chlorobenzoic acid.[22] Treatment of **11** with hot concentrated nitric acid afforded the nitro derivative **12**,[23] which was catalytically reduced by hydrogen transfer to give aminoxanthone **13** in 67% overall yield from xanthone **11**. Acylation of **13** with *N*-Boc-L-proline, previously activated with isobutyl chloroformate, provided a quantitative yield of amide **14**, which was then deprotected to **15** in 82% yield by treatment with trifluoroacetic acid (Scheme 2). Reduction of **15** with sodium borohydride in refluxing ethanol gave amidoxanthydrol **16**, apparently as a mixture of two epimeric alcohols with two rotamers each, the ^{1}H NMR spectrum showing four singlets for benzylic protons between 5.75 and 5.97 ppm. Finally, reaction of this mixture with AcOH at rt smoothly afforded diazepinone (+)-**2** in 70% overall yield from **15**.[24] That this cyclodehydration and that of the open analogue **6c** took place under much milder conditions than those of **6a** and **6b** suggest that this reaction may proceed through an S_N1 type mechanism, with loss of water from C_5 and the formation of a carbocation intermediate that in the cases of **16** and **6c** would be stabilized by the electron-donating substituents.

A distinctive feature of the cyclization of **16** was that it produced just a single stereoisomer, which was identified as the cis derivative **2** by NOE experiments in which irradiation of the singlet at 4.69 ppm (H_{14a}) caused a 1.9% enhancement of the intensity of the doublet at 3.74 ppm (H_{10a}). This difference in stereoselectivity compared with the reactions of the open analogues **6a** and **6c** can be attributed to the more rigid nature of **16**, which leads to the reactions at the two diastereotopic faces of the intermediate xanthylium cation having very different transition states.

In conclusion, we have synthesized enantiopure cis and trans stereoisomers of 5-phenylpyrrolo[2,1-*c*][1,4]benzodiazepine, (−)-**8**, and (−)-**9**, in five steps and 69% overall yield from 2-aminobenzophenone, the key step being a non-stereoselective cyclodehydration; and have also stereoselectively prepared the pentacyclic *cis*-pyrrolo[2,1-*c*][1,4]benzodiazepinone (+)-**2** in six steps from the starting xanthone, in a global yield of 38%.

Acknowledgments

Support of this work by the Spanish Ministry of Education and Science in collaboration with the European Regional Development Fund (through Project CTQ2005-02338), and by the Xunta de Galicia (through Projects PGIDITO6PXIC209067PN and 2007/XA084, and a pre-doctoral grant to L.L.) is gratefully acknowledged.

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17. *(5R,11aS)- and (5S,11aS)-5-phenyl-2,3,5,10,11,11a-hexahydro-1H-pyrrolo[2,1-c]-[1,4]benzodiazepin-11-ones* (**1a**): A solution of amidoalcohol **6a** (370 mg, 1.3 mmol) in dichlorobenzene (12 mL) was deoxygenated with a stream of argon and stirred at 180 °C for 3.5 h in a sealed tube. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (95:5 CH_2Cl_2/MeOH), affording a mixture of the cis and trans diastereoisomers **1a** (1:1 ratio, 311 mg, 86%) as a yellow solid, mp 105–107 °C. IR ($CHCl_3$) 3216 and 3204 (N–H st), 1674 (CO), 1487 (N–H δ). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.77–1.87 and 1.94–2.02 (m, 7H), 2.34–2.44 (m, 2H), 2.58–2.66 (m, 1H), 2,82 (t, J = 6.8 Hz, 1H) and 2.93 (td, J = 8.4, 2.3 Hz, 1H), 3.64 (dd, J = 8.7, 2.8 Hz, 1H, H_{11a}) and 3.77 (d, J = 7.0 Hz, 1H, H_{11a}), 4.69 (s, 1H, H_5) and 5.02 (s, 1H, H_5), 6.58 (d, J = 7.5 Hz, 1H, ArH) and 6.84 (d, J = 7.33 Hz, 1H, ArH), 7.00–7.50 (m, 16H, ArH), 7.60 (br s, 1H, NH) and 7.95 (br s, 1H, NH). ^{13}C NMR/DEPT ($CDCl_3$, 75 MHz), δ (ppm): 23.19 and 24.04 (2 × CH_2), 24.73 and 25.51 (2 × CH_2), 52.17 and 55.71 (2 × CH_2), 60.84 and 60.86 (2 × CH), 66.57 and 75.57 (2 × CH), 121.04 and 122.30 (2 × CH), 124.38 and 125.45 (2 × CH), 127.17 and 127.50 (2 × CH), 127.68 and 127.76 (2 × CH), 128.17 and 128.42 (4 × CH), 128.50 and 128.71 (4 × CH), 129.27 and 131.28 (2 × CH), 133.63 (C), 134.96 (C), 135.29 (C), 137.53 (C), 140.21(C), 145.28 (C), 171.94 (CO), 174.49 (CO). MS (CI), m/z (%): 279 ([M+H]$^+$,100), 278 (M$^+$, 36), 251 (20), 182 (35). MS (EI), m/z (%): 278 (M$^+$, 11), 180 (100). HRMS (EI) calcd for $C_{18}H_{18}N_2O$: 278.1419, found: 278.1411.

18. *Reduction of the diastereomeric mixture of lactams* **1a**: $LiAlH_4$ (88 mg, 2.32 mmol) was added portion-wise to a stirred solution of **1a** (75 mg, 0.27 mmol) in THF (16 mL), and the resulting mixture was heated under reflux for 6 h. After cooling to 0 °C, the solution was neutralized with HCl (1 M), diluted with ice water, and extracted with dichloromethane (3 × 10 mL). The organic extract was washed with brine, dried with Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (95:5 CH_2Cl_2/MeOH) gave a mixture of the two diastereoisomers of **8** (1:0.8 ratio, 58 mg, 81%), and chromatography of this mixture on silica gel (2:8 hexanes/EtOAc) provided (−)-**8** (27 mg, 38%) and (−)-**9** (22 mg, 31%) as amorphous solids:
(−)-(5R,11aS)-5-phenyl-2,3,5,10,11,11a-hexahydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine (**8**): $[\alpha]_D^{20}$ −7.2 (*c* 1, CH_2Cl_2). IR (KBr): 3429 (N–H st), 1631 (N–H δ), 1080 (C–N st) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 1.46–1.54 (m, 1H, $H_{1\alpha}$), 1.67–1.78 (m, 2H, $H_{2\alpha}$, $H_{2\beta}$), 1.93–2.10 (m, 1H, $H_{1\beta}$), 2.34 (q, J = 8.4 Hz, 1H, $H_{3\beta}$), 2.77–2.81 (m, 1H, $H_{3\alpha}$), 2.90–2.95 (m, 1H, $H_{11\alpha}$), 2.98–3.06 (m, 1H, H_{11a}), 3.32 (dd, J = 11.9, 2.9 Hz, 1H, $H_{11\beta}$), 4.86 (s, 1H, H_5), 6.72–6.76 (m, 3H, ArH), 7.00–7.07 (m, 1H, ArH), 7.25–7.28 (m, 1H, ArH), 7.32–7.35 (m, 2H, ArH), 7.42–7.43 (m, 2H, ArH). ^{13}C NMR/DEPT ($CDCl_3$, 75 MHz), δ (ppm): 21.96 (C_2), 28.77 (C_1), 52.33 (C_{11}), 53.23 (C_3), 65.45 (C_{11a}), 70.61 (C_5), 120.07 (CH), 120.87 (CH), 126.87 (CH), 127.46 (CH), 128.04 (2 × CH), 129.29 (2 × CH), 130.77 (CH), 132.78 (C), 142.83 (C), 148.65 (C). MS (CI), m/z (%): 265 ([M+H]$^+$, 100), 206 (2), 187 (2). MS (ESI), m/z (%): 265 ([M+H]$^+$,100). HRMS (ESI, [M+H]$^+$) calcd for $C_{18}H_{21}N_2$: 265.1699, found: 265.1707.
(−)-(5S,11aS)-5-phenyl-2,3,5,10,11,11a-hexahydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine (**9**): $[\alpha]_D^{20}$ −78.5 (*c* 1, CH_2Cl_2). ^{1}H NMR, ($CDCl_3$, 400 MHz), δ (ppm): 1.49–1.57 (m, 1H, $H_{1\beta}$), 1.70–1.87 (m, 2H, $H_{2\alpha}$, $H_{2\beta}$), 1.90–1.98 (m, 1H, $H_{1\alpha}$), 2.82–2.87 (m, 1H, $H_{3\alpha}$), 2.92–3.00 (m, 2H, $H_{11\alpha}$, $H_{11\beta}$), 3.17 (dd, J = 12.9, 2.7 Hz, 1H, $H_{3\beta}$), 3.19–3.25 (m, 1H, H_{11a}), 5.19 (s, 1H, H_5), 6.70 (dd, J = 7.8, 0.8 Hz, 1H, ArH), 6.77 (td, J = 7.4, 1.2 Hz, 1H, ArH), 7.0 (dd, J = 7.5, 1.2 Hz, 1H, ArH), 7.10 (td, J = 7.6, 1.5 Hz, 1H, ArH), 7.20–7.23 (m, 1H, ArH), 7.27–7.30 (m, 2H, ArH), 7.43–7.45 (m, 2H, ArH). ^{13}C NMR/DEPT, ($CDCl_3$, 100 MHz), δ (ppm): 22.52 (C_2), 29.04 (C_1), 51.40 (C_3), 51.93 (C_{11}), 57.01 (C_{11a}), 69.18 (C_5), 118.87 (CH), 119.86 (CH), 126.65 (CH), 127.71 (CH); 127.77 (2 × CH), 129.22 (2 × CH), 129.36 (C), 132.09 (CH), 140.78 (C), 148.41 (C). MS (ESI), m/z (%): 265 ([M+H]$^+$, 100). HRMS (ESI, [M+H]$^+$) calcd for $C_{18}H_{21}N_2$: 265.1699, found: 265.1707.

19. Obtained from D,L-proline and 2-aminobenzophenone as a 1:1 mixture of *cis* and *trans* (±)-**1a**.

20. Prepared in three steps and 78% yield from commercially available 2-amino-5-chloro-2′-fluorobenzophenone.

21. Prepared in three steps and 79% yield from 2-amino-4′-methoxybenzophenone, which was synthesized in 33% overall yield from aniline by conversion to the pivaloylamide, *ortho*-lithiation and trapping with *p*-methoxybenzaldehyde, oxidation with MnO_2 and hydrolysis.

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24. *(+)-(14aR,10aS)-6-methoxy-9,10a,11,12,13,14a-hexahydro-10H-pyrrolo[1,2-a]xanthene[1,9-e,f][1,4]diazepin-10-one* (**2**): $NaBH_4$ (70 mg, 1.85 mmol) was added portion-wise to a stirred solution of amidoxanthone **15** (200 mg, 0.59 mmol) in EtOH (30 mL), and the resulting mixture was heated under reflux for 7 h. After cooling to 0 °C, HCl (10%) was added until gas release ceased, and the solvent was then removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and brine, and the organic layer was washed with water, dried with anhydrous Na_2SO_4, filtered, and concentrated, affording **16** as a mixture of stereoisomers. This crude was dissolved in AcOH (10 mL) and stirred at rt for 72 h. After evaporation of the solvent, water was added (10 mL), followed by a few drops of 5 N NaOH to make a slightly basic solution that was extracted with CH_2Cl_2. The organic extract was washed with brine, dried with Na_2SO_4, filtered, and concentrated. Flash chromatography (SiO_2, 91:9 CH_2Cl_2/MeOH) gave **2** (127 mg, 70%) as an amorphous solid: $[\alpha]_D^{20}$ +48.4 (*c* 1, CH_2Cl_2); IR (KBr) 3433 and 3277 (N–H st), 1673 (CO), 1501 (N–H δ) cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.73–1.79 (m, 2H, $H_{11\alpha}$, $H_{12\beta}$), 2.03–2.05 (m, 1H, $H_{12\beta}$), 2.40–2.43 (m, 1H, $H_{11\alpha}$), 2.62 (q, J = 8.5 Hz, 1H, $H_{13\beta}$), 3.15–3.18 (m, 1H, $H_{13\alpha}$), 3.74 (dd, J = 7.4, 2.1 Hz, 1H, H_{10a}), 3.94 (s, 3H, OCH_3), 4.69 (s, 1H, H_{14a}), 6.74 (d, J = 8.5 Hz, 1H, ArH), 6.89 (d, J = 8.6 Hz, 1H, ArH) 7.09–7.13 (m, 1H, ArH), 7.27–7.33 (m, 3H, ArH), 8.28 (s, 1H, NHCO). ^{13}C NMR/DEPT ($CDCl_3$, 125 MHz), δ (ppm): 23.37 (C_{12}), 23.54 (C_{11}), 51.23 (C_{13}), 54.93 (C_{14a}), 56.59 (OCH_3), 60.84 (C_{10a}), 111.67 (CH), 111.69 (C), 115.32 (CH), 117.60 (CH), 117.70 (C), 119.55 (C), 123.01(CH), 129.20 (CH), 130.34 (CH), 141.61 (C), 146.01 (C), 151.82 (C), 171.92 (CO). MS (EI), m/z (%): 322 (M$^+$, 6), 225 (72), 210 (100). HRMS (EI) calcd for $C_{19}H_{18}N_2O_3$: 322.1317, found: 322.1304.