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

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

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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.

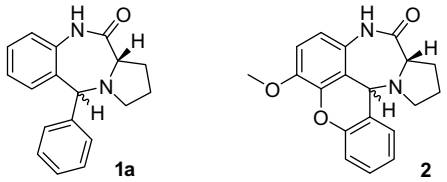

Figure 1. 5-Phenylpyrrolo[2,1-*c*][1,4]benzodiazepin-11-ones.

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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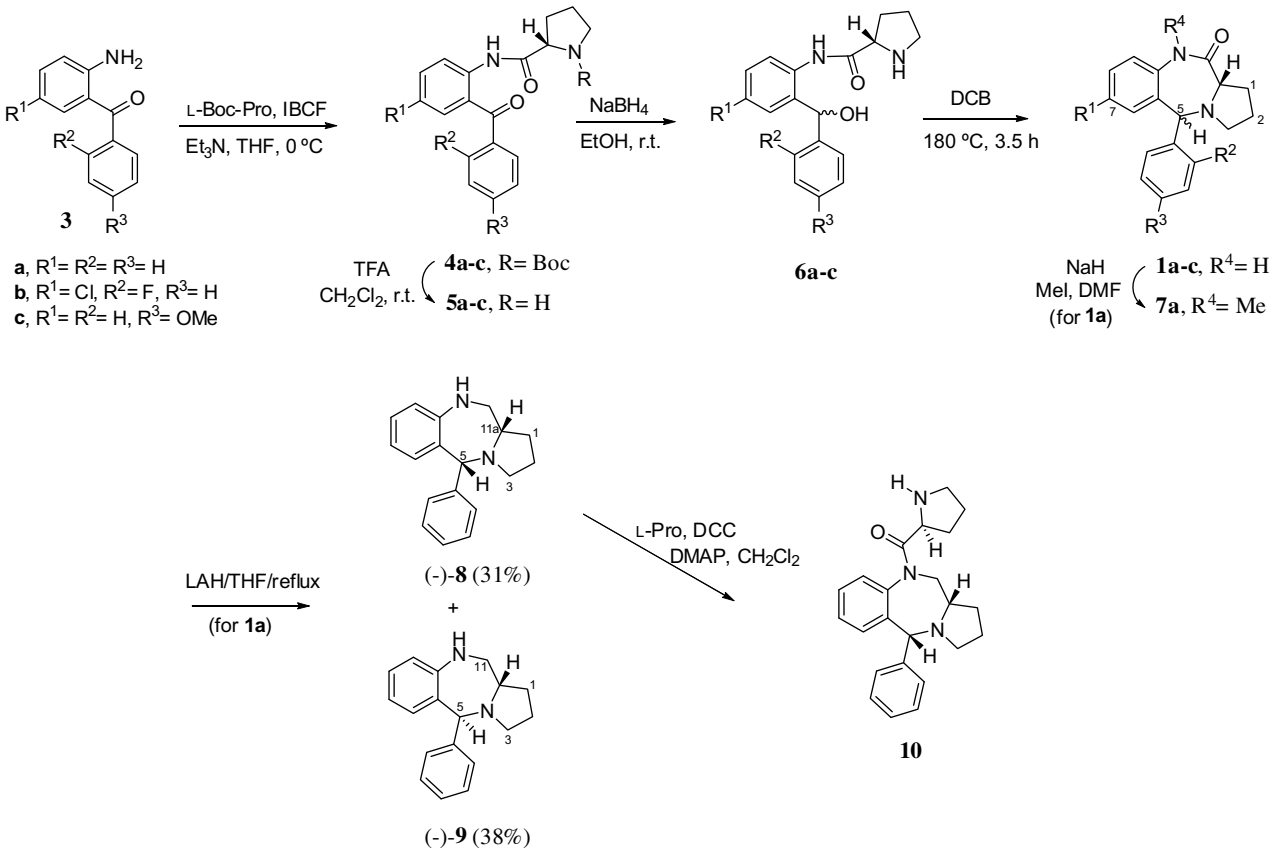

Scheme 1. Synthesis of *cis* and *trans* pyrrolo[2,1-*c*][1,4]benzodiazepines (−)-**8** and (−)-**9**.

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,