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Versatile synthesis of chiral 2-substituted-5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepines as novel scaffolds for peptidomimetic building

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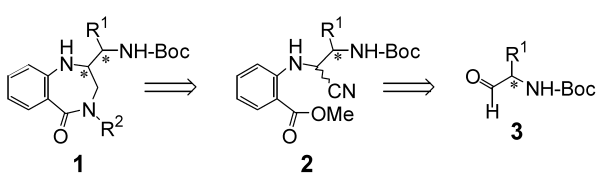
Abstract—The stereocontrolled synthesis of phenylalanine and tryptophan derived 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivatives is described. This new methodology involves a modified Strecker reaction of *N*-Boc protected amino aldehydes and methyl anthranilate, reduction of the resulting α-amino nitriles, and lactamization. The resulting 2-substituted-5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepines were further functionalized at position 4 by alkylation or acylation reactions. One of these new tryptophan-derived 1,4-benzodiazepines showed significant selective binding affinity at cholecystokinin CCK_1 receptors (IC_{50}=156.5±33.2 nM).

1. Introduction

The wide range of biological activities displayed by benzodiazepine derived compounds makes benzodiazepine scaffolds, particularly 1,4-benzodiazepine systems, among the most important privileged structures for drug discovery.[1,2] Thus, in addition to the well-known anxiolytic,[3] sedative,[4] and anticonvulsant[5] activities of the classic benzodiazepines such as diazepam, triazolam or midazolam, several 1,4-benzodiazepine derivatives have demonstrated activity as antitumor antibiotics,[6] anti-HIV agents,[7,8] and antiarrhytmics.[9] Furthermore, diverse 1,4-benzodiazepine derivatives have also been used as constrained dipeptide mimics or non-peptide scaffolds in the search of peptidomimetics either as enzyme inhibitors, such as farnesyltransferase inhibitors,[10,11] or as ligands of G-protein coupled receptors, which include cholecystokinin,[12] fibrinogen,[13] integrin,[14] vasopressin,[15] oxytocin,[16] bradykinin,[17] or *k*-opioid[18] receptors.

In the context of our current interest in methodologies for constructing peptidomimetics, particularly in the search of cholecystokinin receptor ligands, we envisioned a new and versatile access to novel chiral 2,4-disubstituted-5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivatives **1**, from amino acid-derived 2-(methoxycarbonylphenyl)amino nitriles **2**, shown in the retrosynthetic Scheme 1. This strategy involves the application, as key step, of our methodology for the synthesis of amino acid-derived amino nitriles,[19–22] via a modified Strecker reaction, followed by subsequent cyano reduction, lactamization, and introduction of diverse R^2 substitutions into position 4 of the benzodiazepine ring.

We have studied and report herein the applicability of retrosynthetic Scheme 1, first to the preparation of phenylalanine derivatives. Then, taking into account the importance of the tryptophan and the indole ring as privileged structures in the search of cholecystokinin receptor ligands, this methodology was extended to the preparation of tryptophan-derived 1,4-benzodiazepine derivatives.



Scheme 1. Retrosynthesis of 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivatives **1**.

Keywords: 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepines; 1,4-benzodiazepine derivatives; amino acid-derived amino nitriles; peptidomimetics; Strecker synthesis; reduction; lactamization.

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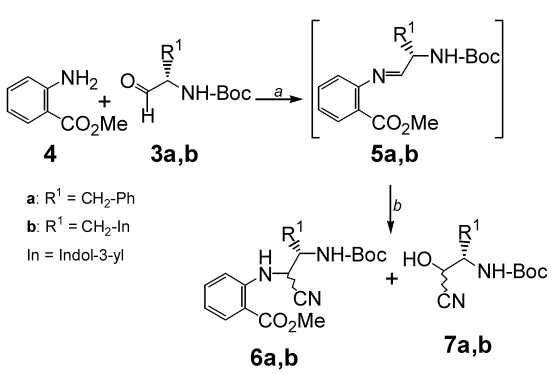
2. Results and discussion

The first step for the synthesis of the proposed 1,4-benzodiazepine derivatives was the preparation of amino nitriles **6a** and **6b** by a modified Strecker reaction of methyl anthranilate (**4**) with the *N*-protected α-amino aldehydes Boc-L-Phe-H (**3a**) and Boc-L-Trp-H (**3b**), respectively, in the presence of trimethylsilyl cyanide (TMSCN) (Scheme 2). Initially, this reaction was carried out applying the reaction conditions developed for the synthesis of Ψ[CH(CN)NH]-pseudopeptides,[19] which involves reaction of an α-amino aldehyde with an amino acid in the presence of $ZnCl_2$ at -20°C for 1 h, followed by in situ reaction with TMSCN for 24 h at 0°C. However, under these conditions, amino nitriles **6a**,**b** were obtained as minor compounds (30%) along with cyanohydrins **7a**,**b** (50%). This result indicated that, due to the lower nucleophilic character of the aniline amino group of **4** in comparison with the amino group of amino acids, a low formation of the imine **5** had occurred when the TMSCN was added, and, therefore, the reaction equilibrium was shifted towards the faster formation of cyanohydrins **7**. The formation of imines **5** was detected by TLC, but they could neither be isolated nor quantified, as they reverted towards methyl anthranilate and the corresponding amino aldehyde **3a** or **3b**.

To improve the yield of amino nitriles **6**, it was necessary to increase the temperature and reaction time for the imine formation up to 65°C and 24 h (Table 1), as well as the temperature of the subsequent in situ reaction with TMSCN, up to room temperature. Under these conditions, amino nitriles **6a** and **6b** were obtained in 81 and 62% yield, respectively, as (1:2) (*R*,*S*)-epimeric mixtures at the new stereogenic center, which could not be resolved. Interestingly, when we tried to obtain the imine **5a** by azeotropic distillation in benzene of a mixture of **3a** and **4**, followed by addition of TMSCN, the amino nitrile **6a** was obtained only in 20% yield within a complex mixture of degradation compounds.

In contrast to our previous experience in the reduction of Ψ[CH(CN)NH]pseudopeptides,[22–24] several attempts to reduce the cyano group in the epimeric mixture of amino nitriles **6a** by catalytic hydrogenation in the presence of 10% Pd(C) gave negative results. Thus, after four days in MeOH at room temperature and 1 atm of H_2 pressure, this amino nitrile mixture was recovered unchanged. When this



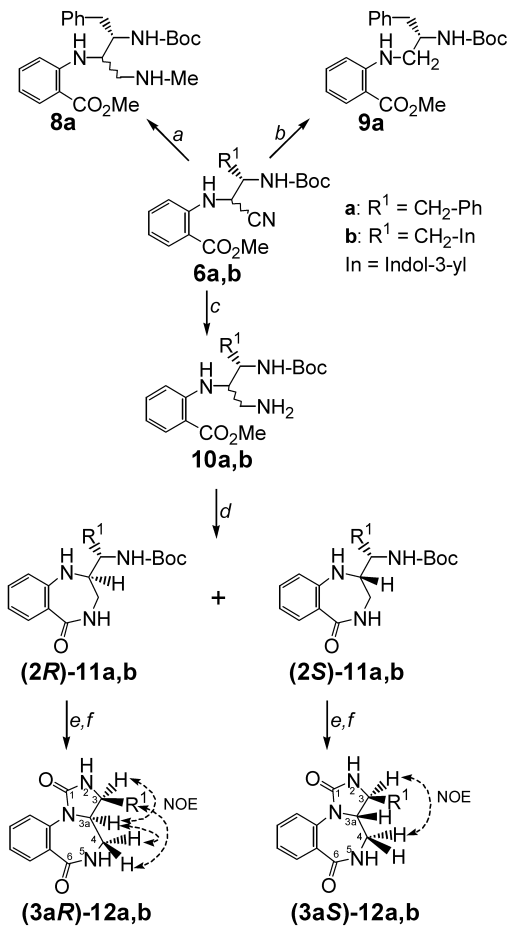
Scheme 2. Synthesis of amino acid-derived 2-(methoxycarbonylphenyl)-amino nitriles. *Reagents*: (a) $ZnCl_2$, MeOH; (b) TMSCN, MeOH.

Table 1. Influence of temperature and time of reaction of **3a** with **4**, before adding TMSCN, upon the yield of the amino nitrile **6a**

Solvent	*T* (°C)	*T* (h)	% **6a**
MeOH[a]	−20	1	30
MeOH[a]	0	1	40
MeOH[a]	20	12	60
MeOH[b]	65	12	81
Benzene[b]	80	12	20

[a] Conditions for the formation of imine **5a**, followed by reaction with TMSCN at 0°C for 24 h.
[b] Conditions for the formation of imine **5a**, followed by reaction with TMSCN at room temperature for 24 h.

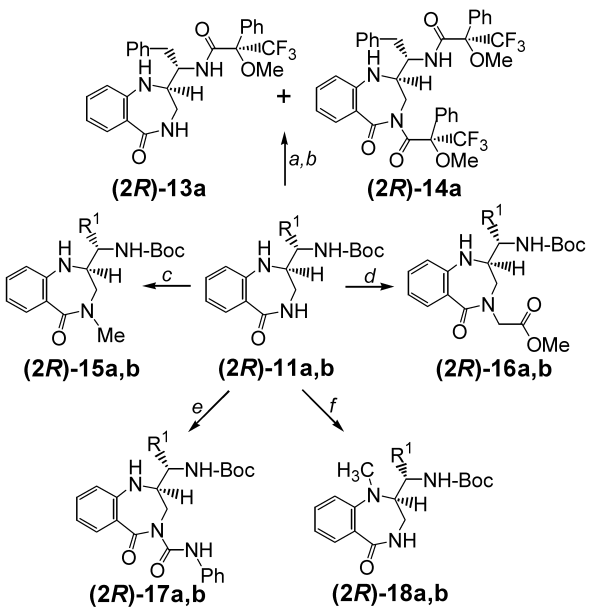
hydrogenation was carried out in the presence of two equivalents of AcOH at 3 atm of H_2 pressure, at either room temperature or 50°C, a complex mixture of degradation compounds was obtained, from which the *N*-methyl amine derivative **8a** (Scheme 3) was the only compound that could be isolated, although in low yield (20%). This compound resulted from the hydrogenation of the cyano group, followed by reaction of the resulting amine with formaldehyde, originated from the MeOH oxidation by the metallic catalyst.[25] Using EtOH as solvent also led to degradation compounds, from which a 12% yield of the hydrogenolysis product **9a** was isolated.



Scheme 3. Synthesis and configuration assignment of 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepines. *Reagents*: (a) H_2, Pd(C), AcOH, MeOH, 50°C; (b) H_2, Pd(C), AcOH, EtOH, 50°C; (c) Raney Ni, NH_2–NH_2·H_2O, MeOH, 65°C. (d) NaMeO, MeOH, 65°C; (e) 2.5N HCl in EtOAc; (f) $(Cl_3CO)_2CO$, TEA, CH_2Cl_2.

As shown in Scheme 3, the cyano reduction of amino nitriles **6a** and **6b** was satisfactorily carried out by Raney nickel catalyzed hydrogen transfer from hydrazine hydrate in refluxing MeOH.[26] Thus, the triamine derivatives **10a** and **10b** were obtained in 94 and 80% yield, respectively. The subsequent treatment of these (2:1) (*R*,*S*)-epimeric mixtures with NaOMe in refluxing MeOH for 7–10 days led to the corresponding 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivatives **11a** and **11b** (87–65%), which were chromatographically resolved in their respective epimers (2*R*)-**11a**,**b** and (2*S*)-**11a**,**b**. To assign the C_2 absolute configuration in these compounds, they were transformed into their 1,6-dioxo-1,2,3,3a,4,5-hexahydro-imidazo[3,4-*a*][1,4]benzodiazepine derivatives (3a*R*)- and (3a*S*)-**12a**,**b**, by *N*-Boc protection removal, followed by reaction with bis(trichloromethyl)carbonate. The NOE effects observed in the DPGSE-NOE spectra of compounds **12a**,**b**, shown in Scheme 3, allowed the assignment of configuration at C_{3a}, and, therefore, at C_2 in **11a**,**b**.

Although no racemization had previously been observed in the synthesis of Ψ[CH(CN)NH]pseudopeptides,[19] it could not be discharged in the synthesis of benzodiazepine derivatives **11**, due to the strong basic conditions needed for the cyano reduction and lactamization steps, and to the higher temperature required for the synthesis of amino nitriles **6**. To clarify this point, the phenylalanine-derived 1,4-benzodiazepine (2*R*)-**11a** was *N*-Boc-deprotected and treated with excess of the Mosher acid chloride [(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride [(*R*)-MTPA-Cl]]. As shown in Scheme 4, this treatment yielded a mixture of the monoamide (2*R*)-**13a** (66%) and the diamide (2*R*)-**14a** (22%). The fact that neither the HPLC analysis nor the ^{1}H NMR spectra of these compounds showed the presence of duplicity of signals discharged the existence of racemization in the synthesis of derivatives **11a**.



Scheme 4. Reactivity of 1,4-benzodiazepine derivatives. *Reagents*: (a) 2.5N HCl in EtOAc; (b) (*R*)-MTPA-Cl, TEA, CH_2Cl_2; (c) MeI, NaH, THF; (d) $BrCH_2CO_2Me$, NaH, THF; (e) Ph-NCO, NaH, THF; (f) 35–40% HCHO in MeOH, $NaBH_3CN$, AcOH, CH_3CN.

The possibility of introducing additional groups regioselectively into position 4 of the 1,4-benzodiazepine ring, either by alkylation or acylation, was studied in both major epimers (2*R*)-**11a** and (2*R*)-**11b** (Scheme 4). The reaction of these compounds with MeI in the presence of NaH led to the corresponding 4-methyl derivatives (2*R*)-**15a**,**b**. In the case of the tryptophan derivative (2*R*)-**11b**, some dimethylation at position 4 and at the indole NH was also observed, depending on the excess of MeI and NaH used. Analogously, the reaction of (2*R*)-**11a** and (2*R*)-**11b** with methyl bromoacetate in the presence of NaH led to the 4-methoxycarbonyl methyl derivatives (2*R*)-**16a** and (2*R*)-**16b**. In this case, no dialkylation was observed in the tryptophan derivative (2*R*)-**11b**. On the other hand, the reaction of (2*R*)-**11a** and (2*R*)-**11b** with an equivalent of phenyl isocyanate in the presence of NaH gave the 4-phenylcarbamoyl derivatives (2*R*)-**17a** and (2*R*)-**17b** selectively. It is worth mentioning that 1,4-benzodiazepine derivatives **16** are *N*- and *C*-orthogonally protected and conformationally restricted tripeptide analogues, which could be used for the introduction of conformational restrictions into larger peptides.

Finally, as many of the biologically active 1,4-benzodiazepine derivatives are substituted at position 1, particularly with a methyl group, such as for example in Devazepide,[27] prototype of CCK_1 cholecystokinin receptor antagonists, we also explored this possibility, which was satisfactorily achieved by reaction of compounds (2*R*)-**11a**,**b** with a 35–40% methanolic solution of formaldehyde and $NaBH_3CN$ in the presence of AcOH, yielding derivatives 2*R*)-**18a**,**b** (Scheme 4, yield >90%).

All new 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivatives **11**–**18a**,**b** were evaluated as CCK_1 and CCK_2 receptor ligands, by measuring the inhibition of the specific [^{3}H]propionyl-CCK-8 binding to rat pancreas and cerebral cortex homogenates,[28] using CCK-8 and the CCK_1 and CCK_2 selective antagonists Devazepide[27] and PD-135, 158[29] as standard compounds. Except for the tryptophan derivative (2*R*)-**11b**, which showed selective affinity for CCK_1 receptors, with an IC_{50} of 156.5±33.2 nM, none of these 1,4-benzodiazepine derivatives showed significant binding affinity for any of both receptor subtypes at concentrations below 10 μM. Compound (2*R*)-**11b** could represent the starting hint for a new family of selective CCK_1 receptor ligands.

3. Conclusion

Herein we report a new efficient and versatile methodology for the synthesis of highly functionalized chiral 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivatives from amino acid-derived amino nitriles, which gives access to a diversity of therapeutically privileged structures.

4. Experimental

4.1. General procedures

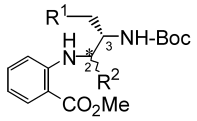
All reagents were of commercial quality. Solvents were

dried and purified by standard methods. Analytical TLC was performed on aluminum sheets coated with a 0.2 mm layer of silica gel 60 F_{254}, Merck. Preparative radial chromatography was performed on 20 cm diameter glass Plate coated with a 1 mm layer of silica gel PF_{254} Merck. Silica gel 60 (230–400 mesh), Merck, was used for flash chromatography. Melting points were taken on a micro hot stage apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 141 polarimeter. ^{1}H NMR spectra were recorded at 300, 400 or 500 MHz, using TMS as reference, and ^{13}C NMR spectra were recorded at 50, 75 or 125 MHz. Elemental analyses were obtained on a CH-O-RAPID apparatus. Analytical RP-HPLC was performed on a Waters μBondapak C_{18} (3.9×300 mm, 10 μm) column, with a flow rate of 1 mL/min, and using a tunable UV detector set at 214 nm. Mixtures of CH_3CN (solvent A) and 0.05% TFA in H_2O (solvent B) were used as mobile phases.

4.1.1. General procedure for the synthesis of amino acid-derived 2-(methoxycarbonyl-phenyl)amino nitriles 6a and 6b. Methyl anthranilate (1.21 g, 8 mmol) and $ZnCl_2$ (0.60 g, 4.4 mmol) were added to a solution of the corresponding amino aldehyde **3a**[19] or **3b**[19] (4 mmol) in MeOH (75 mL), and the mixture was refluxed for 12 h. This reaction mixture was left to cool at room temperature for adding TMSCN (0.60 mL, 4.8 mmol), and the stirring was continued at this temperature for additional 24 h. Then, the solvent was evaporated and the residue was dissolved in EtOAc (75 mL). This solution was successively washed with H_2O (2×25 mL) and brine (25 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography using (1–20%) EtOAc–hexane gradient for **6a** and (0–3%) MeOH gradient in CH_2Cl_2 for **6b** as eluants. The most significant analytical and spectroscopic data of **6a**,**b** are summarized in Table 2.

4.1.2. Synthesis of (2*RS*,3*S*)-3-(*tert*-butoxycarbonyl)-amino-2-(2-methoxycarbonyl)phenylamino-1-methyl-amino-4-phenylbutane (8a). 10% Pd(C) (200 mg) and acetic acid (32 μL, 0.5 mmol) were added to a solution of the amino nitrile **6a** (200 mg, 0.5 mmol) in MeOH (30 mL), and the mixture was hydrogenated at 3 atm of H_2 pressure and 50°C for two days. Afterward, the catalyst was filtered off and washed with MeOH. The filtrate was evaporated, and the residue was purified by flash chromatography using (5–30%) EtOAc–hexane gradient as eluant. Compound **8a** was isolated in 20% yield (43 mg) as a foam. RP-HPLC t_R 8.75 min [μBondapak C_{18}, CH_3CN/0.05% TFA (45:55)]; ^{1}H RMN (300 MHz, $CDCl_3$) δ 1.30 (s, 9H, Boc), 2.18 (s, 3H, N–CH_3), 2.50 (m, 1H, 4-H), 2.66 (dd, 1H, *J*=8, 13.5 Hz, 4-H), 2.75 (m, 2H, 2- and 1-H), 2.97 (dd, 1H, *J*=3, 13.5 Hz, 1-H), 3.74 (s, 3H, O–CH_3), 4.10 and 4.26 (2m, 1H, 3-H), 5.40 and 5.60 (2bs, 1H, *NH*-Boc), 6.50 [t, 1H, *J*=7.5 Hz, 4-H (N–Ph)], 6.58 and 6.78 [2d, 1H, *J*=8 Hz, 6-H (N–Ph)], 7.02–7.30 [m, 6H, 4-Ph and 5-H (N–Ph)], 7.69 and 7.80 (2d, 1H, *J*=7 Hz, 1-NH), 7.82 [dd, 1H, *J*=2, 8 Hz, 3-H (N–Ph)]. Anal. calcd for $C_{24}H_{33}N_3O_4$: C 67.42, H 7.78, N 9.83. Found: C 67.49, H 8.06, N 9.94.

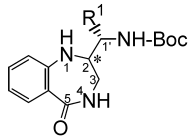
Table 2. Analytical and spectroscopic data of amino nitriles **6a**,**b** and triamine derivatives **10a**,**b**



	[(2*R*)-**6a**+(2*S*)-**6a**]		[(2*R*)-**6b**+(2*S*)-**6b**]		[(2*R*)-**10a**+(2*S*)-**10a**]		[(2*R*)-**10b**+(2*S*)-**10b**]	
R^1	Ph		In		Ph		In	
R^2	CN		CN		CH_2-NH_2		CH_2-NH_2	
(*) Configuration	(*R*)	(*S*)	(*R*)	(*S*)	(*R*)	(*S*)	(*R*)	(*S*)
(2*R*:2*S*)	(1:2)		(1:2)		(2:1)[a]		(2:1)[a]	
Yield (%)	81		62		94		79	
Mp (°C)	Foam		151–155 (EtOAc)		Foam		Foam	
t_R (min)	31.48		29.85		15.05	17.21	11.68	
(A:B)[b]	(40:60)		(40:60)		(35:65)	(35:65)	(35:65)	
Formula[c]	$C_{23}H_{27}N_3O_4$		$C_{25}H_{28}N_4O_4$		$C_{23}H_{31}N_3O_4$		$C_{25}H_{32}N_4O_4$	
^{1}H RMN[d]								
1-H					2.88, 2.95	2.95, 3.05	2.84, 2.95	2.90
2-H	4.30		4.40	4.35	3.68		3.66	
3-H	4.40		4.70	4.60	4.10	4.33	4.24	4.45
3-CH_2	2.90, 3.20	2.98, 3.05	3.10, 3.20	3.25, 3.40	2.90, 2.97	2.78, 2.88	3.08	2.90
NH-Boc	4.70	4.80	4.85		5.20	4.78	5.20	4.84
NH-Ph	8.30		8.30		8.09	8.08	8.12	7.84
OCH_3	3.80	3.77	3.81	3.78	3.86	3.88	3.87	3.88
^{13}C NMR[e]								
C_1	117.19		117.77		42.04	43.04	41.90	43.38
C_2	53.40		52.52		55.61	56.41	52.71	53.76
C_3	48.45	48.10	48.15		53.59	54.67	55.82	56.76
3-CH_2	38.33		24.45		37.36	38.38	27.04	29.24
*CO_2*Me	168.40		168.43		169.06	169.90	169.09	169.70

[a] After the cyano reduction the ligand preference in the CIP notation rules changes.
[b] μBondapak C_{18} (10 μm, 3.9×300 mm), A=CH_3CN, B=0.05% TFA in H_2O.
[c] Satisfactory analyses for C, H, N.
[d] Spectra registered at 300 or 500 MHz in $CDCl_3$, assigned with the help of DQCOSY spectra.
[e] Spectra registered at 50 or 125 MHz in $CDCl_3$, assigned with the help of HMQC spectra.

Table 3. Analytical and spectroscopic data of the 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivatives (2*R*)- and (2*S*)-**11a**,**b**



(2*R*)- and (2*S*)-11a,b

	(2*R*)-**11a**	(2*S*)-**11a**	(2*R*)-**11b**	(2*S*)-**11b**
R^1	CH_2-Ph	CH_2-Ph	CH_2-In	CH_2-In
(*) Configuration	(2*R*)	(2*S*)	(2*R*)	(2*S*)
Yield (%)	61	26	43	21
Formula[a]	$C_{22}H_{27}N_3O_3$	$C_{22}H_{27}N_3O_3$	$C_{24}H_{28}N_4O_3$	$C_{24}H_{28}N_4O_3$
t_R (min) (A:B)[b]	17.88 (30:70)	16.08 (30:70)	18.26 (30:70)	17.63 (30:70)
$[\alpha]_D^{20}$	−105 (*c*, 1 in MeOH)	+129 (*c*, 1 in MeOH)	−93 (*c*, 1 in MeOH)	+63 (*c*, 1 in MeOH)
^{1}H RMN[c]				
1-H	4.65	4.25	3.50	4.00
2-H	3.63	3.65	3.50	3.56
3-H	3.40, 3.45	3.38, 3.49	3.30, 3.40	3.29, 3.38
4-H	7.38	7.18	7.24	6.64
1′-H	4.00	3.90	4.12	3.99
1′-CH_2	2.81, 3.02	2.78, 2.85	3.00	2.96
NH-Boc	4.90	5.03	4.80	4.94
$J_{2,3}$	0 and 6	0 and 6	0 and 7	0 and 7
$J_{3,3}$	13	15	14.5	14.5
$J_{3,4}$	2	3	2	2
^{13}C NMR[d]				
C_2	63.48	61.80	63.31	61.68
C_3	41.02	43.26	41.07	43.58
C_5	172.11	172.00	172.19	171.91
$C_{1'}$	54.54	55.54	53.34	54.19
1′-CH_2	36.92	38.45	26.99	28.22

Isolated as foams.
[a] Satisfactory analyses for C, H, N.
[b] μBondapak C_{18} (10 μm, 3.9×300 mm), A=CH_3CN, B=0.05% TFA in H_2O.
[c] Spectra registered at 400 or 500 MHz in $CDCl_3$, assigned with the help of DQCOSY spectra.
[d] Spectra registered at 50 or 125 MHz in $CDCl_3$, assigned with the help of HMQC spectra.

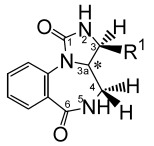
4.1.3. Synthesis of (2*S*)-2-(*tert*-butoxycarbonyl)amino-1-(2-methoxycarbonyl)phenylamino-3-phenylpropane (9a). 10% Pd(C) (200 mg) and acetic acid (32 μL, 0.5 mmol) were added to a solution of the amino nitrile **6a** (200 mg, 0.5 mmol) in EtOH (30 mL), and the mixture was hydrogenated at 3 atm of H_2 pressure and 50°C for two days. Afterward, the catalyst was filtered off and washed with EtOH. The filtrate was evaporated, and the residue was purified by flash chromatography using (5–30%) EtOAc–hexane gradient as eluant. Compound **9a** was isolated in 12% yield (23 mg) as a foam. RP-HPLC t_R 9.96 min [μBondapak C_{18}, CH_3CN/0.05% TFA (45:55)]; ^{1}H RMN (200 MHz, $CDCl_3$) δ 1.45 (s, 9H, Boc), 2.90 (d, 2H, *J*=6 Hz, 3-H), 3.22 (dd, 1H, *J*=5, 13 Hz, 1-H), 3.35 (dd, 1H, *J*=5, 13 Hz, 1-H), 3.90 (s, 3H, O–CH_3), 4.15 (m, 1H, 2-H), 4.63 (d, 1H, *J*=7 Hz, *NH*-Boc), 6.60 [t, 1H, *J*=7 Hz, 4-H (N–Ph)], 6.71 [d, 1H, *J*=7 Hz, 6-H (N–Ph)], 7.13–7.40 [m, 6H, 4-Ph and 5-H (N–Ph)], 7.80 [dd, 1H, *J*=2, 8 Hz, 3-H (N–Ph)], 8.00 (bs, 1H, 1-*NH*). Anal. calcd for $C_{22}H_{28}N_2O_4$: C 68.73, H 7.34, N 7.29. Found: C 68.84, H 7.53, N 7.42.

4.1.4. General procedure for the reduction of amino nitriles 6a,b. Synthesis of 10a and 10b. Raney Ni (900 mg) and hydrazine hydrate (1.94 mL, 40 mmol) were added to a solution of the corresponding amino nitrile **6a** or **6b** (2 mmol) in MeOH (100 mL), and the resulting reaction mixture was refluxed for 1 h. Then, the mixture was filtered through silica gel 60 (230–400 mesh), and the silica was washed with boiling MeOH (5×10 mL).The filtrates were evaporated, and the residue was purified by flash chromatography using (0–5%) MeOH–CH_2Cl_2 gradient as eluant. The most significant analytical and spectroscopic data of **10a**,**b** are summarized in Table 2.

4.1.5. General procedure for the synthesis of 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivatives (2*R*)- and (2*S*)-11a,b. Sodium methoxide (220 mg, 4 mmol) was added to a solution of the corresponding epimeric mixture of triamines **10a** or **10b** (1 mmol) in dry MeOH (75 mL), and the solution was refluxed for 7–10 days. Afterward, the solvent was evaporated and the residue was dissolved in EtOAc (75 mL). The solution was washed with H_2O (20 mL) and brine (25 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography, using (0–5%) MeOH–CH_2Cl_2 gradient as eluant, which also resolved the epimeric mixtures into their respective (2*R*)- and (2*S*)-epimers. The most significant analytical and spectroscopic data of 1,4-benzodiazepine derivatives (2*R*)- and (2*S*)-**11a**,**b** are summarized in Table 3.

4.1.6. General procedure for the synthesis of 1,6-dioxo-1,2,3,3a,4,5-hexahydroimidazo[3,4-*a*][1,4]-benzo-diazepines (3a*R*)- and (3a*S*)-12a,b. A solution of the corresponding 1,4-benzodiazepine derivative (2*R*)- and

Table 4. Analytical and spectroscopic data of the 1,6-dioxo-1,2,3,3a,4,5-hexahydroimidazo[3,4-*a*][1,4]benzodiazepines (3a*R*)- and (3a*S*)-**12a**,**b**



12a,b

	(3a*R*)-**12a**	(3a*S*)-**12a**	(3a*R*)-**12b**	(3a*S*)-**12b**
R^1	CH_2-Ph	CH_2-Ph	CH_2-In	CH_2-In
(*) Configuration	(3a*R*)	(3a*S*)	(3a*R*)	(3a*S*)
Yield (%)	58	46	44	64
Formula[a]	$C_{18}H_{17}N_3O_2$	$C_{18}H_{17}N_3O_2$	$C_{20}H_{18}N_4O_2$	$C_{20}H_{18}N_4O_2$
Mp (°C)	260–262 (MeOH)	180–183 (EtOAc–hexane)	>320 (CH_2Cl_2-MeOH)	Foam
t_R (min) (A:B)[b]	5.71 (30:70)	6.61 (30:70)	6.38 (30:70)	6.68 (30:70)
$[\alpha]_D^{20}$	−143 (*c*, 1 in DMSO)	+34 (*c*, 1 in MeOH)	−6 (*c*, 1 in MeOH)	+29 (*c*, 1 in MeOH)
^{1}H RMN[c]				
2-H	6.81	6.96	6.81	6.95
3-H	4.06	3.84	4.16	3.88
3a-H	4.20	3.81	4.22	3.83
4-H	3.20, 3.42	2.70, 3.08	3.18, 3.48	2.82, 3.10
5-H	8.32	8.20	8.38	8.22
3-CH_2	2.86, 3.04	2.85, 2.90	2.98, 3.20	2.98
$J_{3,3a}$	8	–	8	8
$J_{3a,4}$	0 and 5	0 and 4	0 and 5	0 and 4
$J_{4,4}$	15.5	15	15.5	15
$J_{5,4}$	5 and 7	4 and 7	5 and 7	4 and 7
^{13}C NMR[d]				
C_1	159.84	159.03	160.06	159.23
C_3	54.12	54.51	53.06	54.09
C_{3a}	64.97	65.47	64.83	66.04
C_4	40.10	41.45	40.00	41.73
C_6	170.53	169.96	170.45	170.13
3-CH_2	36.98	39.63	27.04	29.84

[a] Satisfactory analyses for C, H, N.
[b] μBondapak C_{18} (10 μm, 3.9×300 mm), A=CH_3CN, B=0.05% TFA in H_2O.
[c] Spectra registered at 300 MHz in DMSO-d_6, assigned with the help of DQCOSY spectra.
[d] Spectra registered at 50 or 75 MHz in DMSO-d_6, assigned with the help of HMQC spectra.

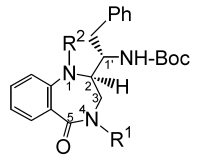
(2*S*)-**11a**,**b** (0.2 mmol) in 2.5N solution of HCl in EtOAc (10 mL) was stirred at room temperature for 2–5 h. This solution was evaporated to dryness, and the residue was dissolved in H_2O (3 mL) and lyophilized. The resulting residue was dissolved in dry CH_2Cl_2 (15 mL), and the solution was cooled to 0°C. Then, TEA (28 μL, 0.2 mmol), bis(trichloromethyl)carbonate (60 mg, 0.2 mmol), and TEA (168 μL, 1.2 mmol) were added successively, and the reaction mixture was stirred at 0°C for 30 min. Afterward, this mixture was diluted with CH_2Cl_2 (15 mL), washed with H_2O (2×10 mL) and brine (2×10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography using (0–6%) MeOH–CH_2Cl_2 gradient as eluant. The most significant analytical and spectroscopic data of (3a*R*)- and (3a*S*)-**12a**,**b** are summarized in Table 4.

4.1.7. Synthesis of the Mosher amide derivatives (2*R*)-13a and (2*R*)-14a. A solution of the 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine (2*R*)-**11a** (15 mg, 40 μmol) in 2.5 N solution of HCl in EtOAc (10 mL) was stirred at room temperature for 2–5 h. This solution was evaporated to dryness, and the residue was dissolved in H_2O (3 mL) and lyophilized. The resulting residue was dissolved in dry CH_2Cl_2 (5 mL), and the solution was cooled to 0°C. Then, TEA (5.8 μL, 40 μmol), (*R*)-MTPA-Cl (11.8 μL, 60 μmol), and TEA (8.7 μL, 60 μmol) were added successively, and the reaction mixture was stirred at 0°C for 30 min. Afterward, this mixture was diluted with CH_2Cl_2 (10 mL), successively washed with saturated $NaHCO_3$ (2×3 mL), H_2O (2×3 mL) and brine (2×3 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography using (0–5%) MeOH–CH_2Cl_2 gradient as eluant, to give the monoamide (2*R*)-**13a** and the diamide (2*R*)-**14a**.

(2R)-2-[(1S)-1-[(R)-1-Methoxy-1-trifluoromethyl-phenyl-acetyl]amino-2-phenylethyl]-5-oxo-1,2,3,4-tetrahydro-5H-1,4-benzodiazepine (2R)-**13a**. White solid (11.0 mg, 52%); $[\alpha]_D^{20}=-23°$ (*c*, 0.1 in $CHCl_3$); mp 190–193°C (EtOAc–hexane). t_R 4.80 min (μBondapak C_{18}; CH_3CN/0.05% TFA 50:50); ^{1}H RMN (300 MHz, $CDCl_3$, 60°C), δ (ppm): 2.69 [dd, 1H, *J*=11, 14 Hz, 2′-H (ethyl)]; 3.06 (s, 3H, O–CH_3); 3.22 [dd, 1H, *J*=4.5, 14 Hz, 2′-H (ethyl)]; 3.27 (dd, 1H, *J*=4, 12 Hz, 3-H); 3.44 (ddd, 1H, *J*=2, 7, 12 Hz, 3-H); 3.58 (m, 1H, 2-H); 4.20 (bs, 1H, 1-H); 4.39 [m, 1H, 1′-H (ethyl)]; 6.48 (t, 1H, *J*=4 Hz, 4-H); 6.59 (d, 1H, *J*=8 Hz, 9-H); 6.81 (t, 1H, *J*=8 Hz, 7-H); 6.88 (d, 1H, *J*=5 Hz, 1′-*NH*); 7.10–7.28 (m, 11H, Ph and 8-H); 7.77 (dd, 1H, *J*=2, 8 Hz, 6-H).

(2R)-4-[(R)-1-Methoxy-1-trifluoromethyl-phenylacetyl]-2-[(1S)-1-[(R)-1-methoxy-1-trifluoromethyl-phenylacetyl]-amino-2-phenylethyl]-5-oxo-1,2,3,4-tetrahydro-5H-1,4-

Table 5. Analytical and spectroscopic data of the phenylalanine-derived 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivatives (2*R*)-**15**–**18a**



(2*R*)- 15-18a

	(2*R*)-**15a**	(2*R*)-**16a**	(2*R*)-**17b**	(2*R*)-**18b**
R^1	Me	CH_2-CO_2Me	CONH–Ph	H
R^2	H	H	H	Me
Yield (%)	82	96	76	94
Formula[a]	$C_{23}H_{29}N_3O_3$	$C_{25}H_{31}N_3O_5$	$C_{29}H_{32}N_4O_4$	$C_{23}H_{29}N_3O_3$
Mp (°C)	84–85 (EtOAc–hexane)	Foam	Foam	Foam
t_R (min) (A:B)[b]	28.16 (30:70)	17.21 (30:70)	5.71 (25:75)	32.41 (25:75)
^{1}H RMN[c]				
1-*R* [2]	4.44	4.32	5.30	3.04
2-H	3.64	4.03	3.89	3.54
3-H	3.24, 3.52	3.40, 3.60	3.64, 4.86	3.46, 3.65
4-*R* [1]	3.04 (Me)	3.70 (OMe) 4.16, 4.35 (CH_2CO_2Me)	11.80 (CONH)	7.31
1′-H	4.00	3.72	4.16	4.44
CH_2-Ph	2.80	2.74, 2.86	2.98, 3.12	2.73, 2.82
NH-Boc	4.75	4.33	6.28	5.80
$J_{2,3}$	0 and 8	0 and 7	0 and 9	4 and 5
$J_{3,3}$	14	14	14	12
^{13}C NMR[d]				
C_2	62.54	62.62	64.46	71.32
C_3	37.55	47.83	42.21	41.04
C_5	169.89	170.37	174.00	172.51
$C_{1'}$	54.84	54.51	57.01	52.17
CH_2-Ph	36.18	37.86	37.85	39.05
R^1	49.39 (Me)	50.83 (OMe) 50.15 (CH_2CO_2Me) 170.15 (CO_2Me)	157.40 (CONH)	–
R^2	–	–		39.34

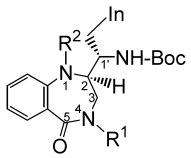
[a] Satisfactory analyses for C, H, N.
[b] μBondapak C_{18} (10 μm, 3.9×300 mm), A=CH_3CN, B=0.05% TFA in H_2O.
[c] Spectra registered at 200 or 300 MHz in $CDCl_3$ for (2*R*)-**15a** and (2*R*)-**16a**, and in $(CD_3)_2CO$ for (2*R*)-**17a** and (2*R*)-**18a**, assigned with the help of DQCOSY spectra.
[d] Spectra registered at 50 or 75 MHz in $CDCl_3$ for (2*R*)-**15a** and (2*R*)-**16a**, and in $(CD_3)_2CO$ for (2*R*)-**17a** and (2*R*)-**18a**, assigned with the help of HMQC spectra.

benzodiazepine (2R)-**14a**. Foam (5.0 mg, 17%); $[\alpha]_D^{20}=-21°$ (*c*, 0.1 in $CHCl_3$). t_R 6.90 min (μBondapak C_{18}; CH_3CN/0.05% TFA 50:50); ^{1}H RMN (300 MHz, $CDCl_3$, 60°C), δ (ppm): 2.82 [dd, 1H, *J*=11, 14 Hz, 2′-H (ethyl)]; 3.04 [dd, 1H, *J*=5, 14 Hz, 2′-H (ethyl)]; 3.10 (s, 3H, O–CH_3); 3.38 (s, 3H, O–CH_3); 3.80 (m, 2H, 3-H); 4.20 (m, 1H. 2-H); 4.41 [m, 1H, 1′-H (ethyl)]; 5.17 (bs, 1H, 1-H); 6.57 (d, 1H, *J*=8 Hz, 9-H); 6.70 (t, 1H, *J*=8 Hz, 7-H); 6.89 [d, 1H, *J*=8 Hz, *NH*(amide)]; 7.00–7.44 (m, 16H, Ph and 8-H); 7.55 (d, 1H, *J*=8 Hz, 6-H).

4.1.8. General procedure for the *N*-alkylation of 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivatives (2*R*)-11a and (2*R*)-11b at position 4. Synthesis of compounds 15a,b and 16a,b. NaH (60% suspension in mineral oil; 20 mg, 0.5 mmol) and the appropriate halide (MeI or $BrCH_2CO_2Me$; 0.5 mmol) were successively added to a solution of the corresponding 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivative (2*R*)-**11a** or (2*R*)-**11b** (0.1 mmol) in dry THF (15 mL), and the resulting reaction mixture was stirred, under argon, at room temperature for a period of 30 min to 48 h. Then, after evaporation of the solvent, the reaction mixture was dissolved in EtOAc (20 mL). This solution was successively washed with H_2O (2×5 mL), 1N HCl ((2×5 mL), H_2O (5 mL), and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography using (0–5%) MeOH–CH_2Cl_2 gradient as eluant. The most significant analytical and spectroscopic data of 1,4-benzodiazepine derivatives (2*R*)-**15a**,**b** and (2*R*)-**16a**,**b** are summarized in Tables 5 and 6.

4.1.9. General procedure for the *N*-acylation of 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivatives (2*R*)-11a,b at position 4. Synthesis of compounds (2*R*)-17a,b. NaH (60% suspension in mineral oil; 4 mg, 0.1 mmol) and phenyl isocyanate (12 μL, 0.11 mmol) were successively added to a solution of the corresponding 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodi-azepine derivative (2*R*)-**11a** or (2*R*)-**11b** (0.1 mmol) in dry THF (15 mL), and the resulting reaction mixture was stirred, under argon, at room temperature for 30 min. Then, after evaporation of the solvent, the reaction mixture was dissolved in EtOAc (20 mL). This solution was successively washed with H_2O (2×5 mL), 1N HCl (2×5 mL), H_2O (5 mL), and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash chromatography using 20% EtOAc in hexane as eluant. The

Table 6. Analytical and spectroscopic data of the tryptophan-derived 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivatives (2*R*)-**15**–**18b**



(2*R*)- 15-18b

	(2*R*)-**15b**	(2*R*)-**16b**	(2*R*)-**17b**	(2*R*)-**18b**
R^1	Me	CH_2–CO_2Me	CONH–Ph	H
R^2	H	H	H	Me
Yield (%)	52	76	56	79
Formula[a]	$C_{25}H_{30}N_4O_3$	$C_{27}H_{33}N_4O_5$	$C_{31}H_{33}N_5O_4$	$C_{25}H_{30}N_4O_3$
t_R (min) (A:B)[b]	6.30 (35:65)	10.36 (30:70)	19.30 (40:60)	9.75 (30:70)
^{1}H RMN[c]				
1-*R* [2]	4.40	4.48	4.72	3.02
2-H	3.75	3.76	3.84	3.62
3-H	3.35, 3.62	3.44, 3.66	3.63, 4.83	3.36, 3.44
4-*R* [1]	3.11 (Me)	3.70 (OMe) 4.11, 4.38 (*CH_2CO_2Me*)	11.77 (CONH)	6.56
1′-H	4.22	4.23	4.26	4.52
CH_2-In	3.05	3.05	3.12, 3.20	2.84, 2.96
NH-Boc	4.50	4.53	4.64	4.40
$J_{2,3}$	4 and 8	2 and 8	5 and 7	6 and 10
$J_{3,3}$	15	14	14	15
^{13}C NMR[d]				
C_2	62.47	62.51	63.03	69.36
C_3	48.39	47.76	41.23	39.91
C_5	173.56	170.35	173.28	171.07
$C_{1'}$	53.76	54.55	54.36	54.50
CH_2-In	27.34	27.41	29.67	28.32
R^1	36.00 (Me)	52.17 (OMe) 49.99 (*CH_2CO_2Me*) 170.20 (CO_2Me)	156.00 (CONH)	–
R^2	–	–	–	40.86

Isolated as foams.
[a] Satisfactory analyses for C, H, N.
[b] μBondapak C_{18} (10 μm, 3.9×300 mm), A=CH_3CN, B=0.05% TFA in H_2O.
[c] Spectra registered at 400 or 500 MHz in $CDCl_3$, assigned with the help of DQCOSY spectra.
[d] Spectra registered at 50 or 125 MHz in $CDCl_3$, assigned with the help of HMQC spectra.

most significant analytical and spectroscopic data of 1,4-benzodiazepine derivatives (2*R*)-**17a** and (2*R*)-**17b** are summarized in Tables 5 and 6.

4.1.10. General procedure for the *N*-methylation of 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivatives (2*R*)-11a,b at position 1. Synthesis of compounds (2*R*)-18a,b. A 35–40% solution of formaldehyde in MeOH (31 μL, 1.1 mmol) was added to a solution of the corresponding 5-oxo-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine derivative (2*R*)-**11a** or (2*R*)-**11b** (0.1 mmol) in CH_3CN (5 mL), which was stirred at room temperature under argon for 5 min. Then, $NaBH_3CN$ (21 mg, 0.3 mmol) and acetic acid (17 μL, 0.3 mmol) were successively added, and the stirring was continued for another 2 h. After that, the solvents were evaporated, and the residue was dissolved in EtOAc (15 mL). This solution was successively washed with H_2O (2×5 mL), 5% aqueous solution of KOH (2×5 mL), H_2O (5 mL), and brine (5 mL), dried over Na_2SO_4, and evaporated to dryness. The residue was purified by radial chromatography using 3% of MeOH in CH_2Cl_2 ((2*R*)-**18a**) and 10–70% gradient of EtOAc in hexane ((2*R*)-**18b**) as eluants. The most significant analytical and spectroscopic data of 1,4-benzodiazepine derivatives (2*R*)-**18a** and (2*R*)-**18b** are summarized in Tables 5 and 6.

Acknowledgements

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