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A novel approach to the synthesis of diaza-bridged heterocycle derivatives

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Abstract—A novel synthetic route of diaza-bridged heterocycles based on natural 3,9-diazabicyclo[3.3.1]non-6-ene scaffold has been accomplished. The synthetic approach consists of a Pictet–Spengler condensation of the L-Dopa–OMe with an appropriate aldehyde, Fmoc–Aa–H, followed by intramolecular lactamization. This approach generated two configurationally distinct products (cis and trans-isomers), increasing the stereochemical diversity of these compounds. The synthesized compounds are potentially useful in the discovery of novel pharmacologically active compounds.

1. Introduction

In the process of identifying of useful scaffolds for medicinal chemistry, one possible approach is the use of diversity pool of natural products as a guideline to generate new templates. Among the natural products subjected to structural modification, tetrahydroisoquinoline alkaloids occupy a special position owing to their biological and pharmaceutical relevance.[1] In fact, some of these natural products, like saframycin, renieramycin, and ecteinascidin families show potent cytotoxic activity against a variety of tumor cell lines in vitro, against several rodent tumors and human tumor xenografts in vivo.[2–4] In all these families, a common 3,9-diazabicyclo[3.3.1]non-6-ene core structure is present (**A** and **B**, Fig. 1). In this context we directed our attention towards the synthesis of new diazatricyclic analogues as scaffold for design of potential antitumoral agents (structure **C**).

The usual strategy for the synthesis of **A** and **B** core structures consists to produce first a (di)ketopiperazine derivative and then to generate an acyl iminium intermediate for the cyclization on an appropriate scaffold.[5,6] Regarding the compounds correlated to scaffold **C**, Koch, Giger, and co-workers reported the synthesis in solution and solid phase of an indole 3,9-diazabicyclo[3.3.1]non-6-en-2-one derivate, starting from L-tryptophan, via sequential Dakin–West/Pictet–Spengler reactions.[7] Nevertheless, this strategy does not allow the formation of the phenolic tricyclic scaffold (structure **C**). More recently, Park et al. described the formation of the phenolic tricyclic scaffold via a sequential cyclic iminium formation and a Pictet–Spengler cyclization under acid condition (Scheme 1). This intramolecular reaction proceeds under strict control of regio- and diastereoselectivity with the formation of a single diastereoisomer.[8]

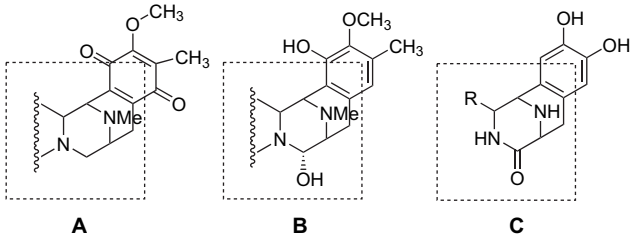

Figure 1. 3,9-Diazabicyclo[3.3.1]non-6-ene core structure present in saframycin and renieramycin (**A**), ecteinascidin (**B**), and the proposed structure 3,9-diazabicyclo[3.3.1]non-6-en-2-one (**C**).

In this communication we report an efficient and improved synthetic methodology to obtain molecules containing the **C** core structure (diaza-bridged heterocycle) starting from enantiopure amino acid derivatives. During the preparation of this manuscript Aubry et al. have reported a similar approach for the synthesis of diaza-bridged heterocycle derivatives.[9]

Keywords: Amino acids; Intramolecular cyclization; Molecular diversity; Antitumor agents.
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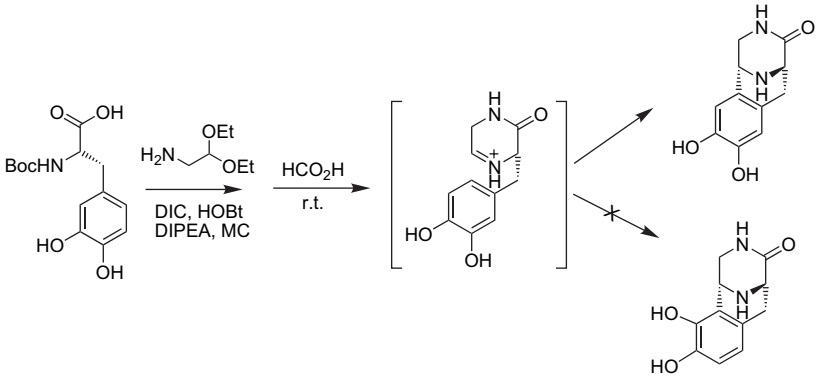
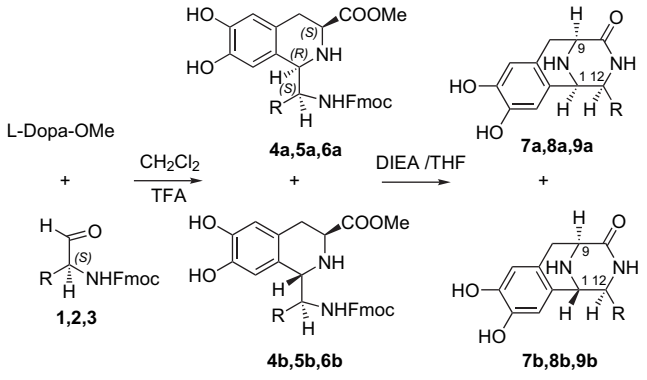


Scheme 1. Formation of the phenolic tricyclic scaffold proposed by Park et al.[8]

2. Results and discussion

Our approach involves the formation of a tetrahydroisoquinoline derivative via Pictet–Spengler[10] reaction between an appropriate enantiopure Fmoc–Aa–H and L-Dopa–OMe, and consecutive intramolecular lactamization to ketopiperazine. Conveniently protected 1,3-disubstituted tetrahydroisoquinolines were initially selected as intermediates for the preparation of the dihydroxydiazatricyclic derivatives. As shown in Scheme 2, compounds **4**–**6** were synthesized via Pictect–Spengler reaction. Accordingly, the Fmoc–Gly–H (**1**), and the enantiomeric pure Fmoc–L-Phe–H (**2**) and Fmoc–L-Ala–H (**3**), prepared from the corresponding Fmoc–L-amino acids reported in literature,[11,12] were condensed with L-Dopa–OMe in dichloromethane to generate the imine intermediates, which were treated with TFA to induce cyclization.[10,12]



Scheme 2. Solution synthesis of diazatricyclic lactam derivatives for **1**,**4**,**7**: R=H; **2**,**5**,**8**: R=CH_3; **3**,**6**,**9**: R=CH_2Ph.

After 6 h of reaction at room temperature, the desired tetrahydroisoquinolines were obtained as diastereoisomeric mixtures **4a**, **b** (a/b=3:2), **5a**, **b** (a/b=3:2), and **6a**, **b** (a/b=1:1) in 48, 50, and 51% yield, respectively. These results suggest that under these conditions, the Pictet–Spengler reaction is not diastereoselective. The diastereoisomeric a/b ratio (cis/trans, relative configuration between C-1 and C-3 protons) were determined from the crude reaction mixtures by HPLC or ^{1}H NMR (Table 1).

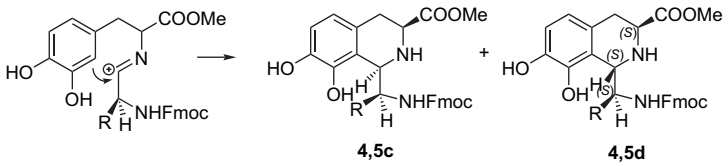
The diastereoisomeric mixture **4**, **5**, and **6** were chromatographically resolved and their configuration at C-1 were confirmed by NMR analysis.[13] In addition, a third series of compounds were also detected and isolated from the crude **4** and **5** (≈10 and 7% yield), while no additional compounds were detected from crude **6**. These additional compounds were identified by NMR analysis as cis and trans mixture of the 1,2,3,4-tetrahydro-7,8-hydroxy-isoquinoline regioisomers **4c**, **4d** (**c**/**d**=3:1) and **5c**, **5d** (**c**/**d**=3:1). The formation of compounds **4c**, **4d** and **5c**, **5d** might be explained by condensation between the iminium ion and the aromatic C-2 by nucleophile reaction (Scheme 3).

When the regioisomeric mixtures **4c**, **4d** and **5c**, **5d** were subjected to further purification process only the cis-regioisomers **4c** and **5c** were isolated as pure (see experimental data). Finally, the diazatricyclic derivatives **7a**, **7b**; **8a**, **8b** and **9a**, **9b** were easily obtained, in quantitative yields, by intramolecular lactamization of the corresponding tetrahydroisoquinolines in condition of cleavage of Fmoc protecting group, using 33% DIEA/THF solution at room temperature. This kind of cyclization, concomitant with removal of the *N*-protecting group, has already been described

Table 1. Tetrahydroisoquinoline (**4**–**6**) and diazatricyclic derivatives (**7**–**9**)

Amino aldehyde	R	Tetrahydroisoquinoline	Yield[a] (%)	a/b Ratio	HPLC[b] t_r (min)	Diazatricyclic derivative	Yield (%)	HPLC[b] t_r (min)
1	H	**4a**	29	1.5:1	24.13	**7a**	91	16.32
		4b	19		24.36	**7b**	92	16.47
2	CH_3	**5a**	28	1.2:1	23.43	**8a**	91	14.86
		5b	23		23.57	**8b**	89	15.21
3	CH_2Ph	**6a**	26	1:1	22.47	**9a**	92	13.72
		6b	25		22.78	**9b**	90	13.98

[a] Isolated yield for chromatographically purified compounds.
[b] Analytical RP-HPLC was performed on a C18 column (Vydac 218TP54) using a gradient of acetonitrile in 0.1% aqueous TFA (10–40%) in 45 min at 1 mL/min.



Scheme 3. Formation of compounds **c** and **d**.

during the *N*-deprotection of Z- and Boc–aminomethylene pseudo-dipeptide methyl esters under catalytic hydrogenation or acidic conditions.[13]

To confirm the relative configuration of the heterocyclic core structures, extensive NMR studies, including ^{1}H COSY, ROESY, HSQC, and HMBC experiments, were carried out on final compounds (see Supplementary information). The C-1 stereochemistry in all compounds was assigned on the basis of ROESY studies (Fig. 2).

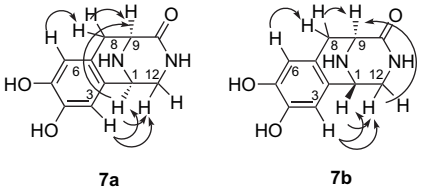


Figure 2. NOEs observed for compounds **7a** and **7b**.

Thus, weak exchanges of magnetization among the H-1 and H-9 protons in compound **7a**, **8a**, and **9a** indicated that these protons were in cis disposition. On the contrary, these NOEs were not observed in the diastereoisomer **7b**, **8b**, and **9b**, in which the H-1 proton has a trans-relationship with respect to the H-9. Since the synthesis starts from DOPA, the absolute configuration at C-9 is *S*, consequently we assigned the configuration as *R* at C-1 in compounds **7**, **8**, and **9a** and as *S* in compounds **7**, **8**, and **9b**. For the cis diastereoisomers other significant NOE effects were observed between H-12′/H-1, H-12′/H-8, H-12′/H-9 (**9a**), and H-12′/H-3 (**8a**) whereas for the trans diastereoisomers, NOE effects were also observed between H-9/H-12 (**8b**, **9b**) and H-3/H-12′ (**8b**) (Table 2).

In the ^{1}H NMR spectra, the main differences between 1*R* (**a**) and 1*S* (**b**)-diastereoisomers were found for the chemical shifts of the H-1 and H-9. Thus, the H-1 and H-9 resonance in compounds having *R* configuration appeared shielded when compared to the same protons in the 1*S*-isomers (0.3–0.8 and 0.2–0.8 ppm). In addition, the C-1 and C-9 resonance in the 1*S* derivatives appear at higher field than the corresponding carbons of the 1*R*-isomers.

The final enantiomeric purity of the synthesized compounds was checked by HPLC analysis using chiral Shiseido Ceramospher RU-2 column, using as gradient acetonitrile/water (90:10)+0.1% diethylamine in 30 min.

Compared to previous synthetic methods described in literature for the preparation of similar bicyclo[3.3.1]nonane systems, this approach contains noteworthy features. In fact, the reaction conditions used allow the formation of two configurationally distinct products (cis and trans-isomers) increasing the stereochemical diversity of these compounds. In addition, this route provides access to the diversification of core skeleton at C-12 starting from synthetically available enantiopure aminoaldehydes.

In conclusion, we have described an efficient synthetic approach to diazatricyclic lactam derivatives, which can be used as core building blocks for combinatorial synthesis as well as for further exploration of their chemistry and pharmaceutical properties. Biological testing of the obtained compounds and the potential diversification of our scaffold is currently under way.

3. Experimental

3.1. General

Reagents, starting material, and solvents were purchased from commercial suppliers and used as received. Analytical TLC was performed on a 0.25 mm layer of silica gel 60 F_{254} Merck and preparative TLC on 20×20 cm glass plates coated with a 2 mm layer of silica gel PF_{254} Merck. Silica gel 60 (300–400 mesh), Merck, was used for flash

Table 2. Significant ^{1}H and ^{13}C NMR data for the diazatricyclic lactam derivatives (**7**, **8**, and **9**)

		7a[a]	**7b**[a]	**8a**[a]	**8b**[a]	**9a**[b]	**9b**[b]
^{1}H NMR	1-H	3.90	4.74	3.82	4.08	3.73	4.03
	8-H	2.50, 2.82	2.86, 3.17	2.58, 2.90	2.73, 3.01	2.72, 3.05	2.78, 3.10
	9-H	3.46	4.22	3.65	3.81	3.51	3.73
	12-H	2.95	3.17	3.77	4.11	3.70	4.21
	$J_{1,12}$	3.6	4.0	1.7	2.0	1.6	2.0
	$J_{8,9}$	5.6	5.2, 0.0	5.6, 0.0	4.9	7.6, 0.0	6.8, 0.0
^{13}C NMR	C-1	48.49	47.54	49.61	48.45	52.46	51.85
	C-8	32.63	29.95	31.32	31.40	31.53	32.04
	C-9	53.37	51.06	58.23	56.40	62.03	59.26
	C-12	50.83	46.86	51.43	53.34	49.62	52.51

[a] Registered in DMSO-d_6.
[b] Registered in CD_3OD.

chromatography (FC). Melting points were taken on a Kofler apparatus and are uncorrected. Optical rotations were determined by a Perkin–Elmer-241MC polarimeter using methanol as solvent. ^{1}H NMR spectra were recorded with a Varian 400 spectrometer, operating at 400 MHz. Chemical shifts are reported in δ values (ppm) relative to internal Me_4Si and J values are reported in Hertz (Hz). Analytical RP-HPLC was performed on a C18 column (Vydac 218TP54) using a gradient of acetonitrile in 0.1% aqueous TFA (10–40%) in 45 min at 1 mL/min. Mass spectra were obtained using a FABMS spectrometer. Starting Fmoc–Gly–H, Fmoc–L-Phe–H, and Fmoc–L-Ala–H were prepared according to the procedure as previously described.[11,12a]

3.2. General procedure for the synthesis of (1*R*,3*S*,1′*S*) and (1*S*,3*S*,1′*S*)-1-[(*N*-fluorenyl)metoxycarbonyl]amino-substituted-3-methoxycarbonyl-1,2,3,4-tetrahydro-6,7-dihydroxyisoquinoline (4–6a and b)

To a solution of Fmoc–L-amino aldehydes **1** or **2** or **3** (3.40 mmol) in dichloromethane (30 mL) were added L-Dopa–OMe (3.40 mmol) and TFA (3.40 mmol), and the mixture was stirred at room temperature for 6 h. Then, the mixture was concentrated in vacuo and dichloromethane was added. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The title compounds were purified by flash chromatography (FC) using different eluent systems.

3.2.1. (1*R*,3*S*) and (1*S*,3*S*)-1-[(*N*-fluorenyl)metoxycarbonyl]aminomethyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-6,7-dihydroxyisoquinoline (4a and 4b). FC AcOEt/*n*-hexane (3/1). Isomer **4a**: 0.47 g, 29%. White solid, mp 145–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67–2.86 (m, 2H, H-4); 3.26 (m, 1H, H-1′); 3.52 (dd, J_1=2.9 Hz, J_2=10.4 Hz, 1H, H-3); 3.72 (s, 3H, OCH_3); 3.80 (m, 1H, H-1″); 3.97 (m, 1H, H-1); 4.35 (m, 2H, CH_2 Fmoc); 4.41 (m, 1H, C*H* Fmoc); 6.60 (s, 1H, H-5); 6.69 (s, 1H, H-8); 7.03–7.18 (m, 2H, aryl); 7.29–7.62 (m, 4H, aryl); 7.64–7.83 (m, 2H, aryl). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.72 (C-4); 43.63 (C-1′); 57.90 (C-1); 67.78 (C-3); 112.43 (C-5); 116.35 (C-8); 122.72, 123.81, 126.56, 127.80, 127.45, 128.30, 130.22, 145.51, 146.71 (aryl), 156.13, 170.49 (C=O). ESMS *m*/*z* calcd for $C_{27}H_{26}N_2O_6$ 474.18, found 474.21.

Isomer **4b**: 0.30 g, 19%. White solid, mp 129–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67–2.86 (m, 2H, H-4); 3.27 (m, 1H, H-1′); 3.51 (dd, J_1=2.9 Hz, J_2=10.4 Hz, 1H, H-3); 3.67 (m, 1H, H-1″); 3.71 (s, 3H, OCH_3); 4.01 (m, 1H, H-1); 4.39 (m, 2H, CH_2 Fmoc); 4.50 (m, 1H, C*H* Fmoc); 6.53 (s, 1H, H-5); 6.67 (s, 1H, H-8); 7.00–7.19 (m, 2H, aryl); 7.24–7.61 (m, 4H, aryl); 7.63–7.82 (m, 2H, aryl). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.72 (C-4); 45.75 (C-1′); 55.86 (C-1); 66.63 (C-3); 111.98 (C-5); 115.24 (C-8); 123.65, 123.81, 125.82, 127.35, 127.69, 128.19, 130.12, 145.42, 146.73 (aryl), 156.03, 171.03 (C=O). ESMS *m*/*z* calcd for $C_{27}H_{26}N_2O_6$ 474.18, found 474.31.

The mixture of the corresponding 1,2,3,4-tetrahydro-7,8-dihydroxyisoquinoline (**4c** and **4d**) was submitted to further purification by FC using AcOEt/*n*-hexane (5/1). Isomer **4c**: 0.05 g, 3%. White solid, mp 113–115 °C. Significant data ^{1}H NMR (400 MHz, CD_3Cl): δ 2.63 (dd, J=11.6 and 15.6 Hz, 1H, H-4); 2.88–2.93 (m, 2H, H-4′and H-1′); 3.36 (dd, J=3.6 and 14.4 Hz, 1H, H-1″); 3.64–3.68 (m, 5H, H-3, and CH_3 ester); 3.98 (m, 1H, H-1); 6.45 (d, J=8.0 Hz, 1H, H-5); 6.62 (d, 1H, H-6). ^{13}C NMR (100 MHz, CD_3OD): 25.70 (C-4); 44.63 (C-1′); 52.60 (C-3); 53.99 (C-1). ROESY data: NOE effects between H-1/H-3, H-4/H-5, and H-1′/H-4 were observed. ESMS *m*/*z* calcd for $C_{27}H_{26}N_2O_6$ 474.18, found 474.23. Mixture **4c** and **4d** 0.11 g, 7%, (**c**/**d** ratio 2:1). ^{1}H NMR **4d** (400 MHz, CD_3Cl, from the **4c**+**4d** mixture): δ 2.58–2.62 (m, J=15.6 Hz, 2H, H-4); 2.91 (m, 1H, H-1′); 3.40 (dd, J=5.8 and 14.3 Hz, 1H, H-1″); 3.72 (s, 3H, CH_3 ester); 3.79 (m, 1H, H-3); 4.03 (m, 1H, H-1); 6.52 (d, J=8.0 Hz, 1H, H-5); 6.64 (d, 1H, H-6).

3.2.2. (1*R*,3*S*,1′*S*) and (1*S*,3*S*,1′*S*)-1-[1′-(*N*-fluorenyl)-metoxycarbonyl]amino]ethyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-6,7-dihydroxyisoquinoline (5a and 5b). FC AcOEt/*n*-hexane (3/1). Isomer **5a**: 0.46 g, 28%. White solid, mp 141–43 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (d, 3H, CH_3); 2.75 (m, 1H, H-4a); 3.07 (m, 1H, H-4b,); 3.70 (m,1H, H-3); 3.85 (s, 3H, OCH_3); 4.30–4.33 (m, 2H, H-1, H-1′); 4.47 (m, 2H, CH_2 Fmoc); 4.78 (m, 1H, C*H* Fmoc); 6.38 (s, 1H, H-5); 6.50 (s, 1H, H-8); 7.10–7.19 (m, 2H, aryl); 7.26–7.59 (m, 4H, aryl); 7.65–7.85 (m, 2H, aryl). ^{13}C NMR (100 MHz, $CDCl_3$): 13.31 (C-2′); 25.43 (C-4); 49.29 (C-1′); 51.42 (ester); 56.40 (C-3); 56.50 (C-1); 112.00 (C-5); 115.26 (C-8); 123.04, 124.79, 125.19, 127.56, 127.92, 128.87, 130.19, 141.70, 144.26, 149.09 (aryl), 155.47 and 174.16 (C=O). ESMS *m*/*z* calcd for $C_{28}H_{28}N_2O_6$ 488.19, found 488.31.

Isomer **5b**: 0.38 g, 23%. White solid, mp 134–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (d, 3H, H2′); 3.15–3.29 (m, 2H, H-4); 3.61 (s, 3H, ester CH_3); 4.02 (m, 1H, H-3); 4.34 (d, J=6.4 Hz, 1H, H-1′); 4.50 (d, J=6.4 Hz, 1H, H-1); 4.45 (m, 2H, CH_2 Fmoc); 4.77 (m, 1H, C*H* Fmoc); 6.51 (s, 1H, H-5); 6.65 (s, 1H, H-8). ^{13}C NMR (100 MHz, $CDCl_3$): 18.27 (C-2′); 23.74 (C-4); 47.40 (C-3); 47.51 (C-1′); 52.64 (ester); 53.42 (C-1); 111.00 (C-5); 114.86 (C-8); 123.21, 124.79, 125.20, 127.43, 127.58, 127.93, 128.67, 128.97, 130.43, 141.68, 144.47, 149.01 (aryl), 154.92 and 174.26 (C=O). ESMS *m*/*z* calcd for $C_{28}H_{28}N_2O_6$ 488.19, found 488.25.

The mixture of the corresponding 1,2,3,4-tetrahydro-7,8-dihydroxyisoquinoline (**5c** and **5d**) was submitted to further purification by FC using AcOEt/*n*-hexane (5/1). Isomer **5c**: 0.03 g, 2%. White solid, mp 124–126 °C. Significant data ^{1}H NMR (400 MHz, CD_3Cl): δ 1.35 (d, 3H, H2′); 2.85 (m, J=15.3 Hz, 1H, H-4); 3.06 (m, 2H, H-4′); 3.70 (m, 1H, H-3); 3.85 (s, 3H, ester CH_3); 4.30–4.33 (m, 2H, H-1, H-1′); 6.33 (d, J=8.0 Hz, 1H, H-5); 6.46 (d, 1H, H-6). ^{13}C NMR (100 MHz, CD_3OD): 13.31 (C-2′); 25.43 (C-4); 49.29 (C-1′); 56.40 (C-3); 56.50 (C-1). ROESY data: NOE effects between H-1/H-3, H-4/H-5, and H-2′/H-4 were observed. ESMS *m*/*z* calcd for $C_{28}H_{28}N_2O_6$ 488.19, found 488.25. Mixture **5c** and **5d** 0.075 g, 5%, (**c**/**d** ratio 2:1). ^{1}H NMR **5d** (400 MHz, CD_3Cl, from the **5c**+**5d** mixture): δ 1.33 (d, 3H, H2′); 3.15–3.29 (m, 2H, H-4); 3.71 (s, 3H, ester CH_3); 3.81 (m, 1H, H-3); 4.20 (m, 1H, H-1′); 4.35 (m, 1H, H-1); 6.50 (d, J=8.0 Hz, 1H, H-5); 6.61 (d, 1H, H-6).

3.2.3. (1*R*,3*S*,1′*S*) and (1*S*,3*S*,1′*S*)-1-[1′-(*N*-fluorenyl)-metoxycarbonyl]amino]phenylethyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-6,7-dihydroxyisoquinoline (6a and 6b). FC $CHCl_3$/MeOH (95/5). Isomer **6a**: 0.49 g, 26%. White solid, mp 165–167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.87–2.95 (m, 2H, H-2′); 2.99–3.08 (m, 2H, H-4); 3.54 (s, 3H, OCH_3); 3.79 (d, *J*=10.0 Hz, 1H, H-3); 4.20 (m, 1H, H-1); 4.27 (d, *J*=8.8 Hz, 1H, H-1′); 4.41 (m, 2H, C*H*$_2$ Fmoc); 4.69 (m, 1H, C*H* Fmoc); 6.60 (s, 1H, H-5); 6.70 (s, 1H, H-8); 7.09–7.22 (m, 4H, aryl); 7.26–7.63 (m, 7H, aryl); 7.65–7.85 (m, 2H, aryl). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.19 (C-4); 38.92 (C-2′); 50.12 (C-3); 54.71 (C-1); 58.34 (C-1′); 113.87 (C-8); 115.65(C-5); 123.20, 124.77, 125.19, 126.11, 127.43, 127.58, 127.93, 128.14, 128.67, 128.97, 130.43, 138.52, 141.68, 144.47, 149.01 (aryl); 153.72 and 173.26 (C═O). ESMS *m*/*z* calcd for $C_{34}H_{32}N_2O_6$ 564.23, found 564.34.

Isomer **6b**: 0.48 g, 25%. White solid, mp 148–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.82(m, 1H, H-4a); 2.87–2.99 (m, 2H, H-2′, H-4b); 3.08 (m, 1H, H-2″); 3.57 (s, 3H, OCH_3); 3.92 (d, *J*=12.4 Hz, 1H, H-3); 4.15–4.22 (m, 2H, H-1 and H-1′); 4.28 (m, 2H, C*H*$_2$ Fmoc); 4.63 (m, 1H, C*H* Fmoc); 6.59 (s, 1H, H-5); 6.63 (s, 1H, H-8); 7.11–7.24 (m, 4H, aryl); 7.28–7.59 (m, 7H, aryl); 7.65–7.80 (m, 2H, aryl). ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.12 (C-4); 40.11 (C-2′); 58.66 (C-1); 58.69 (C-3); 114.98 (C-5); 117.24 (C-8); 122.94, 124.57, 125.19, 126.34, 127.41, 127.58, 127.89, 128.14, 128.67, 128.56, 131.13, 138.12, 141.63, 144.29, 149.00 (aryl); 154.12 and 172.98 (C═O). ESMS *m*/*z* calcd for $C_{27}H_{26}N_2O_6$ 564.23, found 564.39.

3.3. Synthesis of (1*R*,3*S*,1′*S*) and (1*S*,3*S*,1′*S*) 12-substituted-4,5-dihydroxy-11,13-diazatricyclo-[7.3.1.0^{2,7}]trideca-3,5,7-trien-10-one (7–9a and 9b)

To a solution of tetrahydroisoquinoline **4a** or **4b**, or **5a** or **5b** or **6a** or **6b** (0.60 mmol) in dry tetrahydrofuran (7 mL), diethylamine (3 mL) was added and the mixture was stirred at room temperature for 2 h. Then the solution was evaporated under reduced pressure and the corresponding diazatricyclic derivatives (**8a** and **8b**, **9a** and **9b**) were precipitated by treatment of the crude residue with EtOAc/*n*-hexane.

3.3.1. (1*R*,3*S*)-4,5-Dihydroxy-11,13-diazatricyclo[7.3.1.0^{2,7}]trideca-3,5,7-trien-10-one (7a). Purified by FC $CHCl_3$/MeOH (95/5). Oil, 120 mg, 91%. $[\alpha]_D^{20}$ −30.0 (*c*=1.0, acetone). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.49 (m, 1H, H-8,); 2.81 (dd, *J*=5.6 Hz, 1H, H-8′); 2.94 (m, *J*=11.2 Hz, 1H, H-12); 3.45 (d, *J*=5.6 Hz, 1H, H-9); 3.56 (dd, *J*=3.6 Hz, 1H, H-12′); 3.90 (d, *J*=3.6 Hz, 1H, H-1); 6.38 (s, 1H, H-6); 6.50 (s, 1H, H-3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.63 (C-8); 48.49 (C-1); 50.83 (C-12); 53.37 (C-9); 114.19 (C-3); 115.64 (C-6); 124.94 (C-7); 128.58 (C-2); 144.19 (C-4); 144.92 (C-5); 172.33 (C═O). ESMS *m*/*z* calcd for $C_{11}H_{12}N_2O_3$ 220.08, found 220.21.

3.3.2. (1*S*,3*S*)-4,5-Dihydroxy-11,13-diazatricyclo-[7.3.1.0^{2,7}]trideca-3,5,7-trien-10-one (7b). Purified by FC $CHCl_3$/MeOH (95/5). Oil, 0.12 g, 92%. $[\alpha]_D^{20}$ −14.3 (*c*=1.0, acetone). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.83–2.87 (dd, *J*=16.8 and 0.0 Hz, 1H, H-8); 3.14–3.19 (m, 2H, H-8′ and H-12); 3.74–3.78 (dd, *J*=12.2 and 4.0 Hz, 1H, H-12′); 4.21 (d, *J*=5.2 Hz, 1H, H-9); 4.74 (d, *J*=2.0 Hz, 1H, H-1); 6.54 (s, 1H, H-6); 6.69 (s, 1H, H-3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 29.94 (C-8); 46.86 (C-12); 47.54 (C-1); 51.06 (C-9); 114.25 (C-6); 115.26 (C-3); 121.72 (C-7); 121.81 (C-2); 145.51 (C-4); 146.74 (C-5); 166.49 (C═O). ESMS *m*/*z* calcd for $C_{11}H_{12}N_2O_3$ 220.08, found 220.26.

3.3.3. (1*R*,3*S*,1′*S*) 12-Methyl-4,5-dihydroxy-11,13-diazatricyclo[7.3.1.0^{2,7}]trideca-3,5,7-trien-10-one (8a). 0.13 g, 91%. White solid, mp 208–210 °C. $[\alpha]_D^{20}$ −13.6 (*c*=1.2, acetone). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.38 (d, 3H, CH_3); 2.58 (m, 1H, H-8); 2.90 (dd, *J*=5.6 Hz, 1H, H-8′); 3.65 (d, *J*=5.6 Hz, 1H, H-9); 3.77 (d, *J*=1.7 Hz, 1H, H-12); 3.82 (d, *J*=1.7 Hz, 1H, H-1); 6.40 (s, 1H, H-6); 6.51 (s, 1H, H-3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.23 (C-12′); 31.32 (C-8); 49.61 (C-1); 51.43 (C-12); 58.23 (C-9); 113.29 (C-3); 114.64 (C-6); 127.84 (C-7); 129.52 (C-2); 144.25 (C-4); 144.91 (C-5); 172.63 (C═O). ESMS *m*/*z* calcd for $C_{12}H_{14}N_2O_3$ 234.10, found 234.21.

3.3.4. (1*S*,3*S*,1′*S*) 12-Methyl-4,5-dihydroxy-11,13-diazatricyclo[7.3.1.0^{2,7}]trideca-3,5,7-trien-10-one (8b). 0.12 g, 89%. White solid, mp 192–193 °C. $[\alpha]_D^{20}$ +2.7 (*c*=1.2, acetone). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.35 (d, 3H, CH_3); 2.73 (m, 1H, H-8); 3.01 (dd, *J*=4.9 Hz, 1H, H-8′); 3.81 (d, *J*=4.9 Hz, 1H, H-9); 4.08 (d, *J*=2.0 Hz, 1H, H-1); 4.11 (d, *J*=2.0 Hz, 1H, H-12); 6.43 (s, 1H, H-6); 6.49 (s, 1H, H-3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.00 (C-12′); 31.40 (C-8); 48.45 (C-1); 53.34 (C-12); 56.40 (C-9); 114.19 (C-3); 114.64 (C-6); 127.81 (C-7); 129.62 (C-2); 144.15 (C-4); 144.83 (C-5); 171.59 (C═O). ESMS *m*/*z* calcd for $C_{12}H_{14}N_2O_3$ 234.10, found 234.20.

3.3.5. (1*R*,3*S*,1′*S*) 12-Benzyl-4,5-dihydroxy-11,13-diazatricyclo[7.3.1.0^{2,7}]trideca-3,5,7-trien-10-one (9a). 0.17 g, 92%. White solid, mp 259–260 °C. $[\alpha]_D^{20}$ −52.7 (*c*=1.00, acetone). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.84–2.86 (m, 2H, H-8, H-12′); 3.07 (dd, 1H, H-12″); 3.25 (dd, 1H, H-8′); 3.57 (t, *J*=4.0 Hz, 1H, H-9); 4.23–4.26 (m, 2H, H-1, H-12); 6.18 (s, 1H, H-3); 6.53 (s, 1H, H-6); 7.22–7.32 (m, 5H, aryl). ^{1}H NMR (400 MHz, CD_3OD): δ 2.72 (dd, *J*=16 and 0.0 Hz, 1H, H-8); 3.03–3.08 (m, 3H, H-12′, H-12″, H-8′); 3.51 (t, *J*=7.6 Hz, 1H, H-9); 3.70 (d, *J*=6.4 Hz, 1H, H-12); 3.73 (d, *J*=1.6 Hz, 1H, H-1); 6.19 (s, 1H, H-3); 6.47 (s, 1H, H-6); 7.23–7.39 (m, 5H, aryl). ^{13}C NMR (100 MHz, CD_3OD): δ 31.53 (C-8); 40.41 (C-12′); 49.62 (C-12); 52.49 (C-1); 62.03 (C-9); 112.65 (C-3); 114.81 (C-6); 123.68 (C-2); 127.79 (C-7); 126.73, 128.70, 129.31, and 138.31 (C-aryl); 143.92 (C-4); 144.36 (C-5); 172.04 (C═O). ESMS *m*/*z* calcd for $C_{18}H_{18}N_2O_3$ 310.13, found, 310.27.

3.3.6. (1*S*,3*S*,1′*S*) 12-Benzyl-4,5-dihydroxy-11,13-diazatricyclo[7.3.1.0^{2,7}]trideca-3,5,7-trien-10-one (9b). 0.16 g, 90%. White solid, mp 220–221 °C. $[\alpha]_D^{20}$ −37.2 (*c*=1.00, acetone). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.61–2.65 (m, *J*=5.2 and 14.2 Hz, 1H, H-12′); 2.73 (m, 1H, H-12″); 2.87 (m, *J*=17.6 Hz, 1H, H-8); 3.19 (dd, *J*=6.0 Hz, 1H, H-8′); 4.18 (d, *J*=6.0 Hz, 1H, H-9); 4.36 (m, 1H, H-12); 4.50 (d, *J*=4.0 Hz, 1H, H-1); 6.52 (s, 1H, H-6 or H-3); 6.59 (s, 1H, H-3 or H-6); 7.24–7.36 (m, 5H, aryl). ^{1}H NMR (400 MHz, CD_3OD): δ 2.31–2.37 (dd, *J*=9.6 and 13.6 Hz, 1H, H-12′); 2.78 (dd, *J*=16.8 and 0.0 Hz, 1H, H-8); 2.93–3.03 (m, 1H,

H-12″); 3.07–3.13 (dd, J=6.8 Hz, 1H, H-8′); 3.73 (d, J=6.8 Hz, 1H, H-9); 4.03 (d, J=2.0 Hz, 1H, H-1); 4.21 (m, J=4.0 Hz, 1H, H-12); 6.57 (s, 1H, H-6); 6.60 (s, 1H, H-3); 7.20–7.36 (m, 5H, aryl). ^{13}C NMR (100 MHz, CD_3OD): δ 32.04 (C-8); 38.29 (C-12′); 51.85 (C-1); 52.51 (C-9); 59.26 (C-12); 115.11 (C-6); 115.69 (C-3); 121.72 (C-2); 123.74 (C-7); 126.89, 128.92, 129.04, and 136.90 (C-aryl); 143.02 (C-4); 145.80 (C-5); 174.00 (C=O). ESMS m/z calcd for $C_{18}H_{18}N_2O_3$ 310.13, found 310.17.

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Supplementary data

As example are reported the experimental NMR spectral data for final compounds **7a**, **7b** and **9a**, **9b**. Supplementary information associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.010.

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