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NOVEL APPROACHES TO OPTICALLY ACTIVE SUBSTITUTED 4,5-DIHYDRO-1,2,4-TRIAZIN-6(*1H*)-ONES AS CONFORMATIONALLY CONSTRAINED PEPTIDOMIMETICS

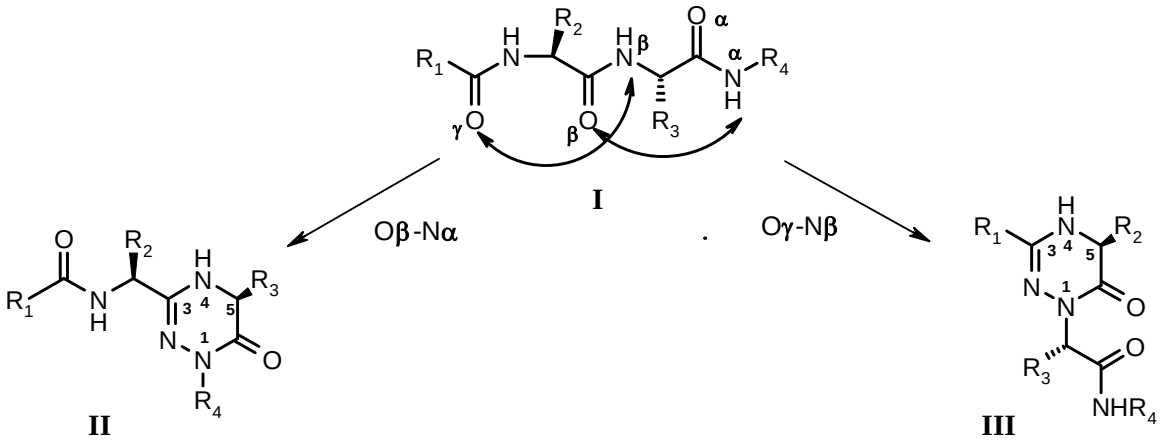
Laurent Sanière, Martine Schmitt, Nadia Pellegrini, and Jean-Jacques Bourguignon*

Laboratoire de Pharmacochimie de la Communication Cellulaire – UMR 7081 du CNRS, Faculté de Pharmacie, 74 route du Rhin, 67400 Illkirch, France

Abstract – Synthesis of 4,5-dihydro-1,2,4-triazin-6-ones bearing different chiral α-amino acid residues at the C3 and N1 positions are reported. Cyclocondensation of *N*-thioacylphthalimides with α-amino hydrazides afforded C3 functionalised dihydrotriazinones in good yields without detectable epimerisation. Moreover, N1-alkylation of the dihydrotriazinone ring with several α-bromo esters was performed with satisfactory yields. Interestingly, this alkylation reaction was found to be regioselective with respect to N4 and NHBoc. This class of compounds represents a new series of small conformationally constrained peptide derivatives.

The characterisation of the physiological role of neuropeptide hormones acting at specific receptors requires the development of efficient pharmacological tools. Among these, the design of small peptides derived from an endogenous ligand is particularly promising.[1,2] In most cases, peptides present a fair to poor bioavailability and are rapidly metabolised by proteases and peptidases,[3,4] whereas short peptides (di and tripeptides) are significantly more stable towards metabolic enzymes. Thus, the challenge for medicinal chemists is the design of small peptides or non-peptidic compounds able to mimic moieties present in the natural peptide ligand. Different structural modifications can be undertaken starting from the backbone of the peptide. Restricting its conformational flexibility in a specific manner might constitute an efficient way to design novel peptidomimetics.[4,5] Thus, a typical type of rigidification was envisaged between nitrogen and oxygen from respectively two consecutive peptidic bonds, as illustrated in Scheme 1. Theoretically, bridging an NH amide onto an sp^2 amidine nitrogen (an amide isostere) leads to chiral dihydrotriazinones **(II)** and **(III)**, bearing an α-amino acid residue in positions 3 and 1, respectively.

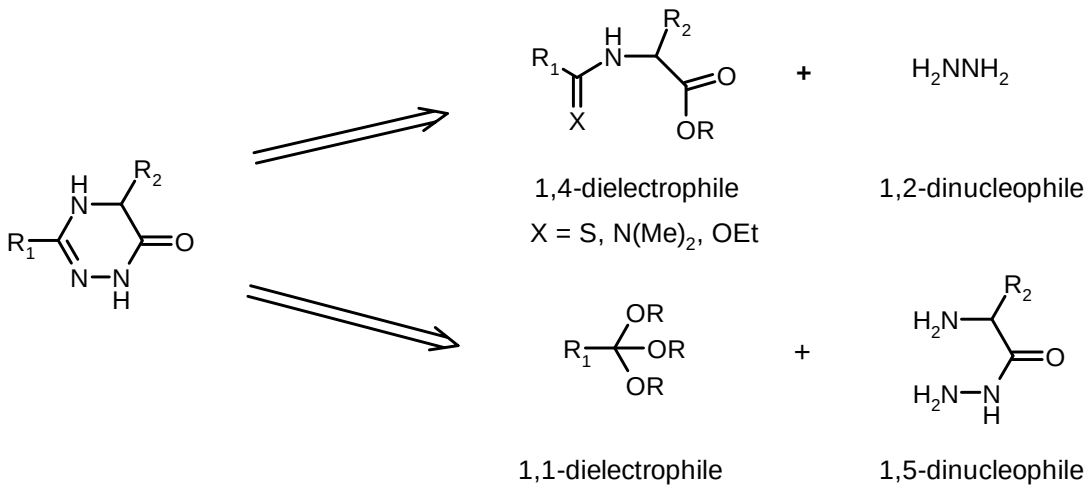
* Corresponding author : Fax : (33) 3 90 24 42 34 / E-mail : jjbpharma.u-strasbg.fr



R_1, R_4 = alkyl, aryl, function or α-amino acid

Scheme 1

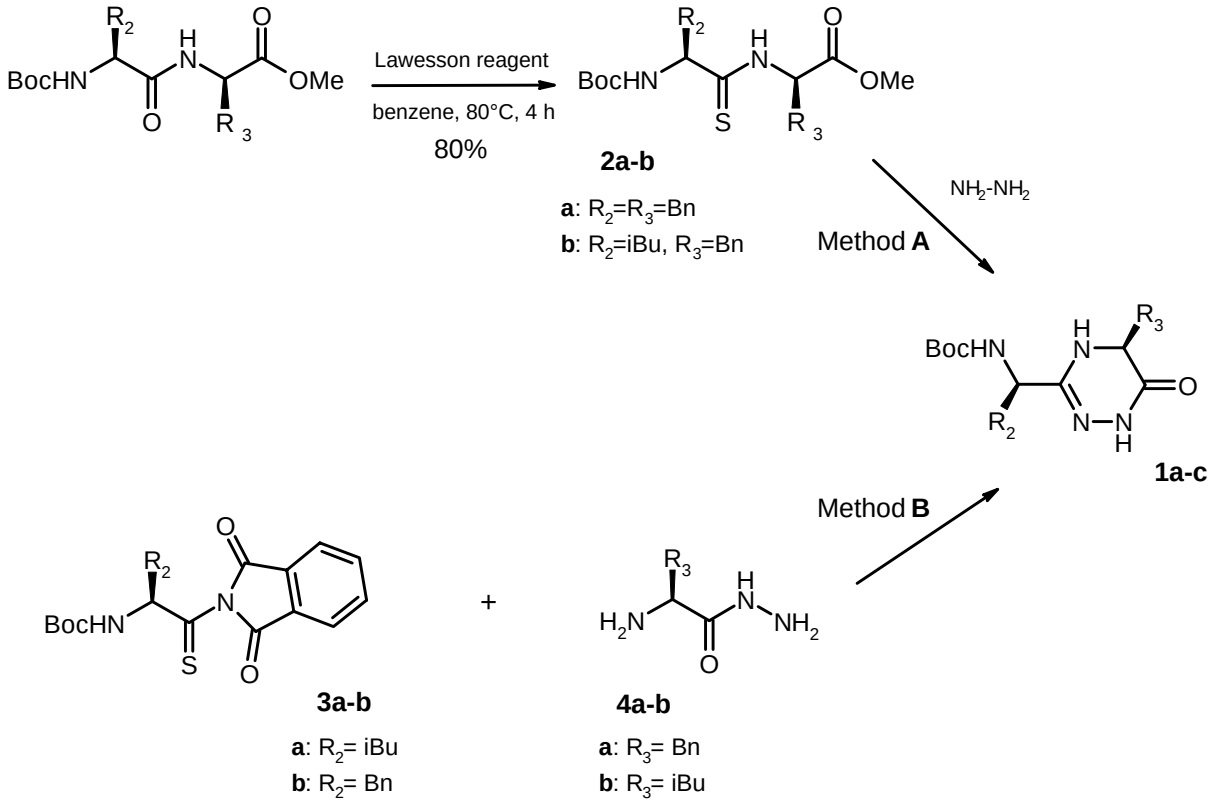
The work reported here describes a novel and versatile preparation of C3 functionalised, optically pure dihydrotriazinones **(II)** *via* a cyclocondensation reaction, and the preparation of several N1 functionalised chiral dihydrotriazinones (**III)** by regioselective N1 alkylation. Different publications describe the synthesis of 1,2,4-triazin-6-ones.[6] However, only a few deal with the preparation of 4,5-dihydro derivatives. The preparation of six-membered heterocycles such as dihydrotriazinones may formally be achieved *via* two different pathways (Scheme 2): condensation of hydrazine, considered as a 1,2-dinucleophile, with a 1,4-dielectrophile (i.e. α-(dimethylaminomethyleneamino)carboxylates,[7,8] α-(ethoxybenzylideneamino)carboxylates,[9] α-isocyanocarboxylates,[10] α-(thioacyl)aminocarboxylates[11]), or cyclocondensation of an α-aminohydrazide (1,5-dinucleophile) onto an orthoester playing the role of a 1,1-dielectrophile.[12]



Scheme 2

The use of α-(thioacyl)aminocarboxylates yields C3 functionalised triazinones.[13] However, the optical purity of the synthesised compounds was not verified.

Recently, Brain *et al.* described the *N*-thioacylphtalimides as efficient *N*-thioacylating agents.[14] Moreover, these compounds easily afforded thiazolines by reaction as an electrophile-nucleophile on the same center, with various β-amino alcohols.[15] These results prompted us to develop an additional reactivity of these synthons: their use as 1,1-dielectrophiles. When prepared from α-amino acids, *N*-thioacylphthalimides may constitute valuable chiral auxiliaries for the preparation of C3 functionalised dihydrotriazinones, not available from orthoesters. Thus, several dihydrotriazinones **(1)** were prepared using either α-(thioacyl)aminocarboxylates **(2)** as a reference literature procedure (Scheme 3, method A), or cyclocondensation of α-aminohydrazides **(4)** with *N*-thioacylphthalimides **(3)** (method B).



Scheme 3

RESULTS AND DISCUSSION

The literature procedure (method A) [11,13] was reinvestigated in order to verify the C5 optical purity after the cyclisation step. Epimerisation of dihydrotriazinone **(1)** would yield a mixture of diastereomers which could be characterised by HPLC.

Preparation of **2** from the corresponding dipeptides was performed in good yields with Lawesson thionation reagent in refluxing benzene. Cyclocondensation of **2** with hydrazine was carried out using thermal[9] or mercury salt catalysed reactions.[13] Excess hydrazine in refluxing dioxane led to **1** in high yields but with significant epimerisation (Table 1, Entries 1, 2). An equimolar amount of hydrazine and a short refluxing time gave a poorer yield but less epimerisation (Entry 3). Finally, the use of mercury diacetate under mild conditions (room temperature) resulted in practically no epimerisation but nevertheless proceeded with satisfactory yields (Entries 4, 5).

The new proposed access to dihydrotriazinones **(1)** (method B) first required the preparation of N-thioacylphtalimides (**3**) from the corresponding primary *N*-Boc-α-aminothioamides, which were then reacted with *o*-phthaloyl dichloride without detectable epimerisation.[14] Compounds **(3)** were reacted with optically pure α-amino hydrazides **(4)** under mild experimental conditions (0°C, 30 min) until total consumption of **4** was observed, as indicated by the disappearance of the typical red color of the thioacyl reagent. Cyclisation conditions were then investigated. Reaction with mercury diacetate at room temperature proceeded without any epimerisation but with poor yield (Entry 6). Optimal results were obtained in refluxing DME over a moderate reaction time. Thus, compounds **(1b-c)** were obtained in modest yields (60-71%) with little epimerisation (less than 5 %, Entries 8, 9, 10).

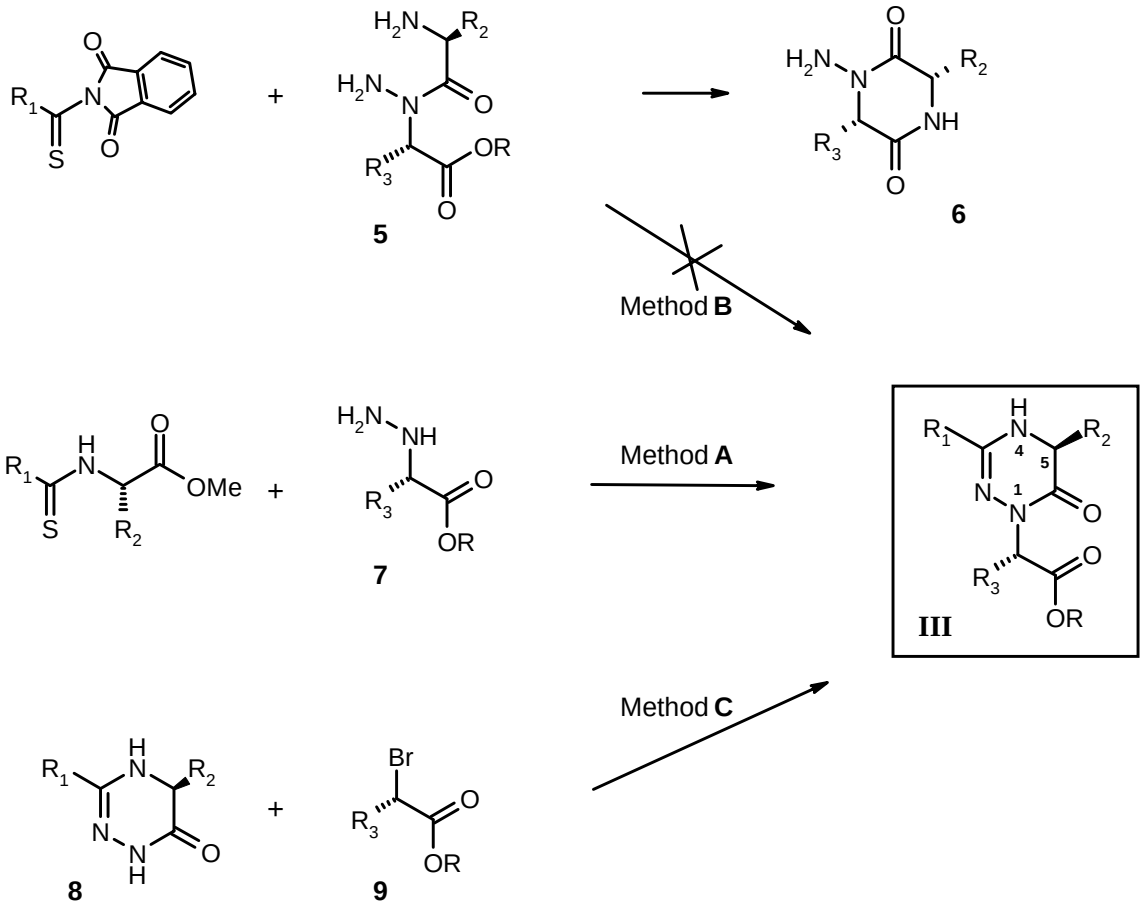
Entry	Path	Compd	R_2	R_3	Nu (mol. eq.)	Solvent	Catalyst	Temp (°C)	Time (h)	Yield (%)	Epimerisation[a] (%)
1	**A**	**1a**	Bn	Bn	5.0	Dioxane	/	100	24	89	22
2	**A**	**1b**	*i*-Bu	Bn	5.0	Dioxane	/	100	24	92	15
3	**A**	**1a**	Bn	Bn	1.0	Dioxane	/	100	2	20	7
4	**A**	**1a**	Bn	Bn	1.2	THF	$Hg(OAc)_2$	25	2	45	0.4
5	**A**	**1a**	Bn	Bn	1.2	THF	$Hg(OAc)_2$	25	27	58	0.4
6	**B**	**1b**	*i*-Bu	Bn	1.0	MeCN	$Hg(OAc)_2$	25	24	30	0.2
7	**B**	**1b**	*i*-Bu	Bn	1.0	MeCN	/	85	4	45	1
8	**B**	**1b**	*i*-Bu	Bn	1.0	DME	/	85	4	71	3
9	**B**	**1a**	Bn	Bn	1.0	DME	/	85	4	60	4
10	**B**	**1c**	Bn	*i*-Bu	1.0	DME	/	85	4	62	nd

a : ratio of diastereomers determined by HPLC
nd : no determined

Table 1

Finally, both methods led to chiral C3 functionalised dihydrotriazinones **(1)** with good and almost similar yields, and negligible or little epimerisation. However, concerning method A, the literature conditions needed to be optimised to avoid epimerisation. A limitation of method A comes from the requirement of a specific dipeptide as a precursor for building in each case the corresponding dihydrotriazinone. In contrast, the new method B would constitute a more versatile approach, as various chiral *N*-thioacylphtalimides **(3)** are easily available and could be cyclocondensed with different hydrazides to yield the corresponding chiral dihydrotriazinones **(1)**.

Concerning the preparation of N1 substituted functionalised dihydrotriazinones **(III)**, we envisaged applying the same methods A and B (Scheme 4).



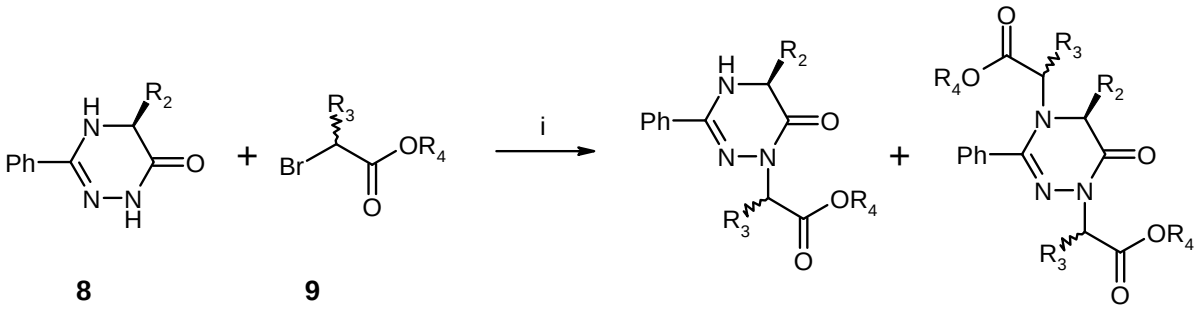
Scheme 4

Unfortunately preparation of the *N*-substituted hydrazide precursor **(5)** required for method B failed, as spontaneous intramolecular cyclisation of **5** occurred leading to diketopiperazine **(6)**, as described recently.[16] Moreover a patent procedure reports the synthesis of related compounds using method A,[17] but

in our hands, the reaction did not proceed as described. Indeed, a preliminary study of the condensation of α-(thioacyl)aminocarboxylates with methyl- and benzylhydrazine as models of substituted hydrazine **(7)** led to poor yields (15-20 %).[18] Thus attempts with *N*-functionalised hydrazines **(7)** were abandoned.

Recently we have reported a new method of alkylating N1 and N4 of dihydrotriazinones using various alkyl halides.[19] This procedure allows a regiocontrolled N1-alkylation of chiral dihydrotriazinones with retention of C5 optical purity. These results prompted us to envisage N1-alkylation of chiral dihydrotriazinones using α-bromo esters **(9)**. This approach constituted an alternative pathway to dihydrotriazinones **III** (Scheme 4, method **C**).

Non-commercially available α-bromo esters **(9)** were prepared either from the corresponding α-amino acids by action of sodium nitrite and potassium bromide in acidic medium[20] followed by esterification,[21] or by treatment of the corresponding α-hydroxy esters with phosphorous tribromide.[22]



8

a : R_2 = Me
b : R_2 = Bn
c : R_2 = iBu

9

a : R_3 = H, R_4=Et
b : R_3 = H, R_4=Bn
c : R_3 = Me, R_4=Et
d : R_3 = Bn, R_4=Et

10a-g + **11a-g**

i: NaH, DMF, N_2,O°C

Scheme 5

When compounds **(9)** were reacted with dihydrotriazinones **(8)** in DMF in the presence of sodium hydride as a base, the expected N1- monosubstituted dihydrotriazinones **(10)** were obtained (Scheme 5). However, some N1,N4- disubstituted derivatives **(11)** could be observed as side products, especially when alkylation was performed with ethyl α-bromoacetate **(9a)** (R_3=H). Thus, in the case of **8a**, a mixture of unreacted starting material (24%) and mono- and dialkyl derivatives **(10)** and **(11)** in almost similar ratio was obtained (46/30, Entry 1, Table 2). This ratio was not sensitive to steric hindrance at C-5 of dihydrotriazinone **8** (compare Entries 1 and 2). It is noteworthy, however, that combining the steric hindrance of both the reactants increased the relative amount of the N1- monoalkyl vs. N1,N4- dialkyl derivatives (Entries 4 and 1). The separation of mono- (**10a**) and disubstituted compounds **(11a)** could not

be achieved by chromatography. However, replacement of the ethyl ester of **9a** by a benzyl ester (**9b**) allowed both more steric hindrance (compare Entries 3 and 2) and easier purification (Entries 3, 5). For large scale preparation of the glycine derivatives **(10c** and **10e)**, a slight excess of sodium hydride and **9b** (1.5 eq) was used in order to fully consume the starting material and thus increase the overall yield (Entries 3, 5, note c). It is noteworthy that, while yields observed using ethyl bromoacetate are satisfactory, the course of the reaction is quite unexpected, (a significant amount of both **10** and **11**) compared to the high regioselectivity of N1 alkylation previously obtained with other primary alkyl halides in our earlier work.[19]

Entry	Compd **8**	Compd **9**	Compd **10** & **11**	R_2	R_3	R_4	yield of **10** [a] (%)	yield of **11** [a] (%)
1	**a**	**a**	**a**	Me	H	Et	46[b]	30[b]
2	**b**	**a**	**b**	Bn	H	Et	33[b]	28[b]
3	**b**	**a**	**c**	Bn	H	Bn	34 (44[c])	12 (32[c])
4	**b**	**c**	**d**	Bn	Me	Et	62[d]	10
5	**c**	**b**	**e**	iBu	H	Bn	34 (46[c])	21 (34[c])
6	**c**	**d**	**f**	iBu	Bn	Et	53[d]	9
7	**c**	**c**	**g**	iBu	Me	Et	61[d]	8

a: 1.1 eq of α-bromoacetate, NaH, DMF, N_2, 0°C
b: ratio **10**:**11** determined by ^{1}H-NMR
c: 1.5 eq of α-bromoacetate was used
d: equimolar mixture of diastereomers (ratio determined by HPLC)

Table 2

However, when ethyl (*RS*)-2-bromopropionate **(9c)** and ethyl (*RS*)-3-phenyl-2-bromopropionate **(9d)** were reacted with **8** under similar conditions, the N1-monosubstituted compounds **(10d**, **10f** and **10g)** were obtained in good yields (Entries 4, 6, 7), and formation of disubstituted compounds **(11)** was not significant. This could be due to the increased steric hindrance of the secondary alkyl halides.

Taking into account that under our experimental conditions no epimerisation occurred at the C-5 center,[19] the compounds **10** were systematically obtained as a mixture of two diastereomers (equimolar ratio determined by HPLC). Both diastereomers were isolated by chromatography and characterised by their HPLC retention time. An optically active ethyl 2-bromopropionate (91% optically pure as determined by ^{1}H-NMR using europium tris[3-(heptafluoropropylhydroxymethylene-(+)-camphorate] as chiral lanthanide shift reagent) was also used as alkylating agent. Even with this chiral agent, a mixture of

diastereomers was still obtained in a ratio of 65:35 (determined by HPLC of the crude reaction mixture), supporting the hypothesis that significant racemisation occurred during alkylation step

The techniques developed for the preparation and alkylation of dihydrotriazinones served as models for building highly substituted dihydrotriazinones **(IV)** (Scheme 6). These compounds can be considered as tripeptide mimetics as they present three chiral centers bearing R_1, R_2 and R_3 substituents. Thus, a similar synthetic approach was developed starting from diastereomerically pure dihydrotriazinone **(1a)**.

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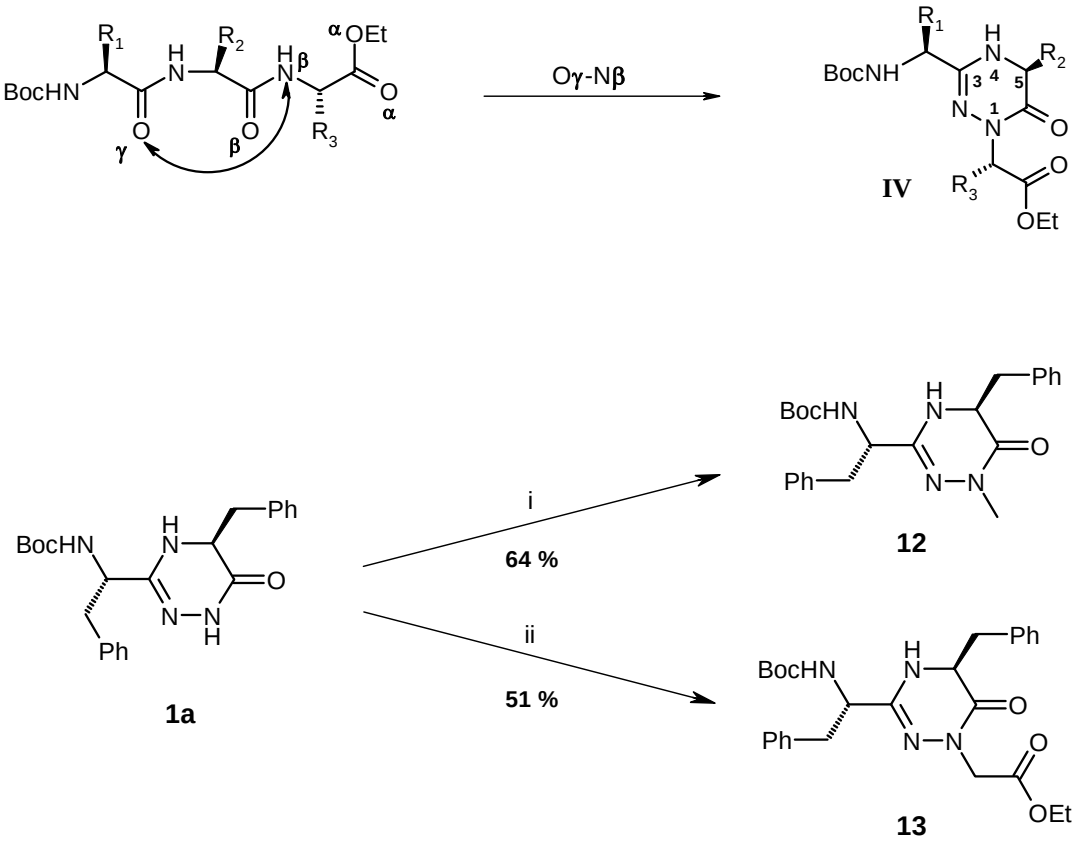

i : MeI, NaH, DMF; ii : ethyl 2-bromoacetate, NaH, DMF.

Scheme 6

In order to characterise the regioselectivity of alkylation (N1/N4/NHBoc), **1a** was reacted with methyl iodide in basic medium (NaH/DMF). These conditions are typical NHBoc alkylation procedures.[23] However, the expected N1- methyl derivative **(12)** was obtained in satisfactory yield (64%, Scheme 6). In a similar manner, the use of ethyl bromoacetate provided the N1- alkyldihydrotriazinone **(13)** in comparable yield (50%). In particular, no dialkylated derivative could be detected in the reaction medium.

As suggested before, this reflects the existence of increased steric hindrance at N4, as the result of the presence of bulky substituents at C-3 of the triazinone ring of **1a**.

CONCLUSION

Finally, three types of chiral dihydrotriazinones bearing typical α-amino acid residues have been prepared. The synthesis of C3 functionalised, optically pure dihydrotriazinones highlights a novel use of *N*-thioacylphtalimides. Their condensation with α-amino hydrazides may constitute a versatile combinatorial chemistry approach leading to scaffold diversity with retention of optical activity.

Moreover, the regioselective N1-alkylation of the dihydrotriazinone ring with primary halides appears to be an efficient and non-epimerising method. In order to increase the scope of the reaction, α-branched ($R_3 \neq H$) esters (e.g. **9c,d**) were successfully introduced. The reactions were not diastereoselective but separation of the diastereomers could be easily achieved. In addition, alkylation was still N1 regioselective vs N4 and NHBoc. These methods will be helpful in developing small peptides and peptidomimetics of pharmacological and therapeutic interest.

EXPERIMENTAL SECTION

Dimethylformamide (DMF) was dried over 4Å molecular sieves. Column chromatography was performed on Merck silica gel 60 (230-400 mesh). ^{1}H- and ^{13}C- NMR spectra were recorded on Bruker AC-200 or DPX-300-Avance spectrometer. Shifts are given in ppm (δ) with respect to the TMS signal and coupling constants (J) are given in Hz. Melting points were measured with a Mettler FP62 apparatus. A Perseptive-Biosystem Mariner mass spectrometer was used to obtain electrospray (ES) spectra. Specific rotations were recorded on a Perkin-Elmer 241-MC polarimeter in the indicated solvent (Na lamp, 589 nm). High-performance liquid chromatography (HPLC) was performed on Kontron-420 gradient pumps equipped with a Kontron-460 autosampler and a Kratos-783 UV detector with tunable wavelength set at 220 nm. Mobil phases were: H_2O (0.1% TFA) and MeOH or MeCN. Columns used: Zorbax, RP-18, 5μm, 4.6x250 mm and Vydac, RP-18, 10 μm, 4.6x250 mm. Elution conditions given are always those found to allow full separation of putative diastereomers.

α-Aminohydrazides **(4)**, ethyl bromoacetate **(9a)**, benzyl bromoacetate **(9b)**, and ethyl 2-bromopropionate **(9c)** were purchased from Senn Chemicals and Aldrich. *N*-Thioacylphtalimides **(3)** were synthesised as described[12] and all compound data are reported therein.

General procedure for the preparation of thioacyldipeptides (2)

Lawesson thionation reagent (0.61 g, 1.5 mmol) was added to a solution of Boc-(*L*)-Phe-(*L*)-Phe-OMe or Boc-(*L*)-Leu-(*L*)-Phe-OMe (3.0 mmol) in benzene (30 mL), under an argon atmosphere. The mixture was heated under reflux for 4 h, then evaporated in *vacuo*. The residue was chromatographed on silica gel.

Boc-(*L*)-Phe-ψ(CSNH)-(*L*)-PheOMe (2a)

82% yield (Eluent : hexane/ethyl acetate, 4/1). Yellow oil used without further purification. $[\alpha]_D$= +99.1° (c= 2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 9H, C(CH_3)$_3$); 3.1-3.4 (m, 4H, 2x CH_2-Ph); 3.66 (s, 3H, OCH_3); 4.5-4.6 (m, 1H, -CO-C*H*-CH_2); 5.2-5.3 (m, 1H, -CS-C*H*-CH_2); 7.0-7.1 (m, 12H, Ar-H.); 7.2-7.5 (m, 9H, Ar-H); 7.88 (d, 1H, J=6.2 Hz, -CH-N*H*-CS exchange with D_2O).

Boc-(*L*)-Leu-ψ(CSNH)-(*L*)-PheOMe (2b)

96% yield (Eluent : hexane/ethyl acetate, 7/1). Pale Yellow solid used wihtout purification, mp : 70-71°C (EtOH) (lit. 73-75°C), $^{13}[\alpha]_D$= +37.0° (c= 1, MeOH) (lit. +39°)[13].^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9-1.0 (m, 6H, J=6.6 Hz, CH-(CH_3)$_2$); 1.47 (s, 9H, C(CH_3)$_3$); 1.6-1.8 (m, 3H, CH_2-C*H*-(CH_3)$_2$); 3.35 (AB part of ABX, 2H, J_{AB}=13.9 Hz, J_{AX}=6.2 Hz, J_{BX}=5.1 Hz, Δδ=0.21, CH_2-Ph); 3.78 (s, 3H, OCH_3); 4.36 (X part of ABX, 1H, J_{AX}=6.3 Hz, J_{BX}=5.0 Hz, C*H*-CH_2-Ph); 5.0-5.1 (m, 1H, N*H* exchange with D_2O); 5.4-5.5 (m, 1H, -CS-C*H*-CH_2); 7.1-7.2 (m, 2H, Ar-H); 7.3-7.5 (m, 3H, Ar-H); 8.2-8.3 (m, 1H, -CH-N*H*-CS exchange with D_2O).

General procedure for the synthesis of C-3 functionalised dihydrotriazinones (1) :

Method A : To a mixture of thioacyldipeptides **(2)** (0.68 mmol) in the appropriate solvent (8 mL) (see Table 1), was added hydrazine hydrate (0.022 g, 0.68 mmol, Table 1) in the presence or absence of mercury diacetate (0.22g, 0.68 mmol, Table 1). Reaction temperatures and times are listed in Table 1 for each case. After removal of the solvent in vacuo, the crude mixture was chromatographed on silica gel (hexane/ethyl acetate, 1/1) to provide compounds **(1)**.

Method B : To a solution of *N*-(thioacyl)phtalimide **(3)** (0.5 mmol) in dimethoxyethane (5 mL) at 4°C, was added dropwise α-amino hydrazide **(4)** (0.5 mmol) in DME (3 mL), under an argon atmosphere. The mixture was kept at 0°C for 30 min, then heated under reflux for 4 hours and evaporated in *vacuo*. The residue was chromatographed on silica gel (hexane/ethyl acetate, 1/1) to provide compounds **(1)**.

5-(*S*)-Benzyl-3-[(*S*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-2-phenethyl]-4,5-dihydro-1,2,4-triazin-6-(1*H*)-one (1a)

60% yield. White solid, mp : 158-161°C (petrolum ether), $[\alpha]_D$= -53.7° (c=4.8, $CHCl_3$). HPLC: R_t= 22.5 min (Zorbax, isocratic: water/MeCN 60/40, flow : 1 mL/min). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 9H, C(C*H*$_3$)$_3$); 2.7-3.3 (m, 4H, 2x C*H*$_2$-Ph); 3.9-4.2 (m, 2H, 2x C*H*-CH$_2$); 4.94 (d, 1H, J=7.8 Hz, N4*H* exchange with D_2O); 5.1-5.2 (m, 1H, N*H*Boc exchange with D_2O); 6.9-7.4 (m, 10H, Ar-H); 8.15 (s, 1H, N1*H* exchange with D_2O). ^{13}C-NMR (300 MHz, $CDCl_3$) δ 28.4 (C(*C*H$_3$)$_3$); 39.2 and 39.9 (2x *C*H$_2$-Ph); 54.3 and 55.0 (2x *C*H-CH$_2$); 80.5 (*C*(CH$_3$)$_3$); 127.2, 128.8, 129.3 and 129.5 (Ar-*CH*.); 135.9 and 137.0 (2 Ar-C-); 147.9 (N-*C*=N-); 156.2 (N-*C*OO-); 162.8 (N-*C*O-CH-). Anal. Calcd for $C_{23}H_{28}N_4O_3$: C, 67.63; H, 6.91, N ; 13.72. Found: C, 67.15 ; H, 6.62 ; N, 13.51.

5-(*S*)-Benzyl-3-[(*S*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-3-(methyl)butyl]-4,5-dihydro-1,2,4-triazin-6-(1*H*)-one (1b)

71% yield. White solid, mp : 64-66°C (petrolum ether), $[\alpha]_D$= -67.9° (c=2, $CHCl_3$). HPLC: R_t= 31.6 min (Zorbax, isocratic: water/MeOH 40/60, flow : 1 mL/min). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.9-1.0 (m, 6H, CH(C*H*$_3$)$_2$); 1.4-1.8 (m, 12H, C*H*$_2$-C*H*(CH$_3$)$_2$ and C(C*H*$_3$)$_3$); 3.11 (AB part of ABX, 2H, J_{AB}=13.9 Hz, J_{AX}=8.9 Hz, J_{BX}=3.2 Hz, Δδ=0.37, C*H*$_2$-Ph); 4.0-4.1 (m, 1H, N-C*H*-CH$_2$-CH); 4.25 (X part of ABX, 1H, J_{AX}=8.9 Hz, J_{BX}=3.2 Hz, C*H*-CH$_2$-Ph); 4.76 (d, 1H, J=7.0 Hz, N*HBoc* exchanged with D_2O); 5.42 (br s, 1H, N4*H* exchange with D_2O); 7.1-7.4 (m, 5H, Ar-H.); 8.31 (br s, 1H, N1*H* exchange with D_2O). ^{13}C-NMR (300 MHz, $CDCl_3$) δ 22.0 and 23.1 (CH(*C*H$_3$)$_2$); 24.8 (*C*H(CH$_3$)$_2$); 28.4 (C(*C*H$_3$)$_3$); 39.8 and 40.8 (*C*H$_2$-Ph + *C*H$_2$-CH(CH$_3$)$_2$); 50.5 (N-*C*H-CH$_2$-CH); 54.9 (*C*H-CH$_2$-Ph); 81.1 (*C*(CH$_3$)$_3$); 127.3, 129.0 and 129.7 (Ar-*CH*.); 136.2 (Ar-C-); 146.3 (N-*C*=N-); 156.8 (N-*C*OO-); 163.5 (N-*C*O-CH-). Anal. Calcd for $C_{20}H_{30}N_4O_3$: C, 64.15; H, 8.07; N, 14.96. Found: C, 64.38 ; H, 8.46 ; N, 14.41.

3-[(*S*)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-phenethyl]-5-(*S*)-isobutyl-4,5-dihydro-1,2,4-triazin-6-(1*H*)-one (1c)

62% yield. White solid, mp : 60-61°C (petrolum ether), $[\alpha]_D$= -24.5° (c=0.1, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.8-0.9 (m, 6H, CH(C*H*$_3$)$_2$); 1.4-1.8 (m, 12H, C*H*$_2$-C*H*(CH$_3$)$_2$ and C(C*H*$_3$)$_3$); 3.13 (d, 2H, J=7.3 Hz, C*H*$_2$-Ph); 3.9-4.0 (m, 1H, C*H*-CH$_2$-Ph); 4.3-4.4 (m, 1H, N-C*H*-CH$_2$-CH); 5.21 (d, 1H, J=6.1 Hz, N4*H* exchange with D_2O); 7.2-7.4 (m, 5H, Ar-H.); 8.10 (br s, 1H, N1*H* exchange with D_2O). ^{13}C-NMR (200 MHz, $CDCl_3$) δ 21.7 and 23.6 (CH(*C*H$_3$)$_2$); 24.1 (*C*H(CH$_3$)$_2$); 28.7 (C(*C*H$_3$)$_3$); 42.1 and 42.5 (*C*H$_2$-Ph +

CH_2-CH(CH_3)$_2$); 51.7 (N-*C*H-CH_2-CH); 51.9 (*C*H-CH_2-Ph); 80.9 (*C*(CH_3)$_3$); 127.3, 129.1 and 129.5 (Ar-CH); 137.5 (Ar-C-); 149.1 (N-*C*=N-); 156.6 (N-*C*OO-); 164.2 (N-*C*O-CH-). Anal. Calcd for $C_{20}H_{30}N_4O_3$: C, 64.15; H, 8.07; N, 14.96. Found: C, 63.62 ; H, 8.05 ; N, 15.04.

Preparation of 4,5-dihydrotriazinones (8)

The title compounds were prepared according to a reported procedure.[11]

3-Phenyl-5-(*S*)-methyl-4,5-dihydro-1,2,4-triazin-6-(*1H*)-one (8a)

56 % yield. White solid, mp : 198-199°C (EtOH) (lit. 194°C)[11]. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.53 (d, 3H, J=6.7 Hz, -CH-C*H*$_3$) ; 4.22 (qd, 1H, J_{CH-CH3}=6.7 Hz, J_{CH-NH}= 1.5 Hz, -C*H*-CH_3) ; 5.0-5.1 (m, 1H, N4*H* exchange with D_2O) ; 7.4-7.5 (m, 3H, Ar-H.) ; 7.6-7.7 (m, 2H, Ar-H.) ; 8.4 (s, 1H, N1*H* exchange with D_2O).

5-(*S*)-Benzyl-3-phenyl-4,5-dihydro-1,2,4-triazin-6-(*1H*)-one (8b)

52 % yield. White solid, mp : 208-210°C (EtOH), $[\alpha]_D$= -81.0° (c=1.6, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.15 (AB part of ABX, 2H, J_{AB}=13.9 Hz, J_{AX}= 10.2 Hz, J_{BX}=3.1 Hz, Δδ=0.50, C*H*$_2$-Ph); 4.33 (m, 1H, -C*H*-CH_2); 5.01 (s, 1H, N4*H* exchange with D_2O); 7.2-7.6 (m, 10H, Ar-H); 8.69 (s, 1H, N1*H* exchange with D_2O). Anal. Calcd for $C_{20}H_{30}N_4O_3$: C, 72.43 ; H, 5.69 ; N, 15.83 . Found: C, 72.72 ; H, 5.81; N, 15.14.

5-(*S*)-Isobutyl-3-phenyl-4,5-dihydro-1,2,4-triazin-6-(*1H*)-one (8c)

55 % yield. White solid, mp : 145-148°C (EtOH), $[\alpha]_D$= -33.7° (c=2, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.0-1.1 (m, 6H, CH(C*H*$_3$)$_2$); 1.2-1.3 (m, 1H, CH_2-C*H*(CH_3)$_2$); 1.6-1.9 (m, 2H, C*H*$_2$-CH(CH_3)$_2$); 4.0-4.2 (m, 1H, NH-C*H*-CH_2); 5.05 (s, 1H, N4*H* exchange with D_2O); 7.3-7.7 (m, 5H, Ar-H); 8.21 (s, 1H, N4*H* exchange with D_2O). Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.50 ; H, 7.41 ; N, 18.17. Found: C, 67.41; H, 7.88 ; N, 17.73.

Preparation of ethyl 2-(*R,S*)-bromo-3-phenylpropionate (9d)

To a solution of (*R,S*)-phenylalanine (4 g, 24.2 mmol) in 25 mL of aqueous sulfuric acid (1.25 M) at 0°C, was added potassium bromide (8.6 g, 72.6 mmol) and then sodium nitrite (1.67 g, 24.2 mmol) in several portions. The mixture was stirred at rt for 1 h, then extracted with dichloromethane, and extract was dried over Na_2SO_4, filtered and evaporated in *vacuo*. The crude oily residue (4.0 g) was dissolved in benzene

(10 mL) under an argon atmosphere, and dimethylformamide *N*,*N*-diethylacetal (16.5 mL, 96.8 mmol) was added dropwise. The mixture was heated under reflux for 30 min, cooled and washed with a Na_2CO_3 saturated solution, then with brine and dried over Na_2SO_4. After removal of the solvent, the crude residue was distilled under vacuum to yield 2.9 g (65%) of a colorless oil used wtihout further purification (bp : 170°C at 10 mbar). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.23(t, 3H, J=7.1 Hz, CH_2-C*H*$_3$); 3.35 (AB part of ABX, 2H, J_{AB}=13.7 Hz, J_{AX}= 7.9 Hz, J_{BX}=7.2 Hz, Δδ=0.22, C*H*$_2$-Ph); 4.18 (q, 2H, J=7.1 Hz, OC*H*$_2$); 4.40 (X part of ABX, 1H, J_{AX}= 7.9 Hz, J_{BX}=7.1 Hz, C*H*-CH_2-Ph); 7.2-7.4 (m, 5H, Ar-H) according to literature analytical data.[24]

Method C : **General procedure for the synthesis of N-1 functionalised dihydrotriazinones (10)** :
To a solution of 4,5-dihydrotriazinone **(8)** (0.80 mmol) in dry DMF (5 mL), at 0°C under a nitrogen atmosphere, was added α-bromo ester **(9)** (0.96 mmol) followed by a dispersion of sodium hydride in mineral oil (w/w 60%, 0.038 g, 0.96 mmol). The mixture was kept at 10°C for 4 h, then diluted with 60 mL of water, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and evaporated in *vacuo*. The crude residue was chromatographed on silica gel.

Ethyl (5-(*S*)-Methyl-6-oxo-3-phenyl-1,4,5,6-tetrahydro[1,2,4]triazin-1-yl)acetate (10a)
46% yield (Eluent : hexane/ ethyl acetate 3/1). Colorless oil, $[\alpha]_D$ = +13.3° (c=0.6, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.32 (t, 3H, J=7.1 Hz, OCH_2-C*H*$_3$); 1.55 (d, 3H, J=6.7 Hz, -CH-C*H*$_3$); 4.2-4.4 (m, 3H, OC*H*$_2$-CH_3 + C*H*-CH_3); 4.55 (s, 2H, NC*H*$_2$); 5.18 (s, 1H, N4*H* exchange with D_2O); 7.3-7.5 (m, 3H, Ar-H); 7.6-7.7 (m, 2H, Ar-H.). ^{13}C-NMR (300 MHz, $CDCl_3$) δ 14.3 (OCH_2-*C*H_3) ; 19.5 (CH-*C*H_3) ; 49.5 (*C*H-CH_3) ; 50.5 (N-*C*H_2); 61.4 (O-*C*H_2-CH_3); 126.3, 128.9, 130.7 (Ar-CH.); 132.3 (Ar-C-); 146.0 (N-*C*=N); 163.3 (CH-*C*O-N); 168.6 (*C*OOCH_2). MS m/z 275.12 $(M+23)^+$

Benzyl (5-(*S*)-Benzyl-6-oxo-3-phenyl-1,4,5,6-tetrahydro[1,2,4]triazin-1-yl)acetate (10c)
34% yield (Eluent : hexane/ethyl acetate 2/1).White solid, mp : 122-124°C (isopropyl ether), $[\alpha]_D$ =-70.9° (c=6.2, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.13 (AB part of ABX, 2H, J_{AB}=13.9 Hz, J_{AX}= 11.3 Hz, J_{BX}=3.0 Hz, Δδ=0.23, C*H*$_2$-Ph); 4.33 (X part of ABX, 1H, J_{AX}= 11.3 Hz, J_{BX}=3 Hz, J_{NH}=2.25 Hz, C*H*-CH_2-Ph); 4.64 (AB, 2H, J_{AB}=16.9 Hz, Δδ=0.09, N-C*H*$_2$); 4.94 (br s, 1H, N4*H* exchange with D_2O); 5.24 (s, 2H, COOC*H*$_2$); 7.2-7.5 (m, 15H, Ar-H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ 39.0 (*C*H_2-Ph); 50.5 (*C*H-CH_2-Ph); 55.1 (N-*C*H_2); 67.2 (O-*C*H_2-Ph); 126.2, 127.4, 128.4, 128.7, 128.8, 128.9, 129.1, 129.7, 130.7,

131.8 (Ar-CH); 135.6 and 136.4 (Ar-C-); 145.4 (N-*C*=N); 162.3 (CH-*C*O-N); 168.5 (*C*OOCH$_2$). Anal. Calcd for $C_{25}H_{23}N_3O_3$: C, 72.62; H, 5.61; N, 10.16. Found: C, 72.62; H, 5.72; N, 10.23.

Ethyl 2-(5-(*S*)-Benzyl-6-oxo-3-phenyl-1,4,5,6-tetrahydro[1,2,4]triazin-1-yl)priopionate (10d)

Two diastereomers were isolated : 62 % overal yield (Eluent : hexane/ethyl acetate 2/1).

HPLC: R_{t1}=27.6 min (Vydac, gradient: H_2O/MeOH: 30 min [98/2 - 0/100], flow: 1 mL/min). Colorless oil, $[\alpha]_D$ = -69.7° (c=5.9, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.26 (t, 3H, J=7.1 Hz, OCH$_2$-*CH$_3$*), 1.62 (d, 2H, J=7.3 Hz, NCH-C*H$_3$*), 3.10 (AB part of ABX, 2H, J_{AB}=13.7 Hz, J_{AX}= 11.0 Hz, J_{BX}=3.4 Hz, Δδ=0.4, C*H$_2$*-Ph); 4.1-4.3 (m, 3H, OC*H$_2$*-CH$_3$ + C*H*-C*H$_2$*-Ph); 5.02 (br s, 1H, N4*H* exchange with D_2O); 5.36 (q, 1H, J=7.3 Hz, N*CH*-CH$_3$); 7.2-7.6 (m, 10H, Ar-H). ^{13}C-NMR (200 MHz, $CDCl_3$) δ 14.6 and 14.8 (OCH$_2$-*C*H$_3$ + NCH-*C*H$_3$); 38.7 (*C*H$_2$-Ph); 54.4, 55.6 (N*C*H-CH$_3$+*C*H-CH$_2$-Ph); 61.7 (O-CH$_2$-*C*H$_3$); 126.4, 127.7, 130.0, 130.8 (Ar-CH); 136.7 (Ar-C-); 145.1 (N-*C*=N); 162.3 (CH-*C*O-N); 171.4 (*C*OOCH$_2$). Anal. Calcd for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 68.98 ; H, 6.55 ; N, 11.10.

HPLC: R_{t1}=24.5 min (Vydac, gradient H_2O/MeOH: 30 min [98/2 - 0/100], flow: 1 mL/min). White solid, mp : 95-97°C (isopropyl ether), $[\alpha]_D$ = -131.7° (c=4.3, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.25 (t, 3H, J=7.1 Hz, OCH$_2$-*CH$_3$*); 1.56 (d, 2H, J=7.1 Hz, NCH-C*H$_3$*); 3.05 (AB part of ABX, 2H, J_{AB}=13.7 Hz, J_{AX}=9.8 Hz, J_{BX}=3.4 Hz, Δδ=0.36, C*H$_2$*-Ph); 4.1-4.4 (m, 3H, OC*H$_2$*-CH$_3$ + C*H*-C*H$_2$*-Ph); 5.28 (q, 1H, J=7.3 Hz, N*CH*-CH$_3$); 7.2-7.6 (m, 10H, Ar-H). ^{13}C-NMR (200 MHz, $CDCl_3$) δ 14.6, 15.0 (OCH$_2$-*C*H$_3$ + NCH-*C*H$_3$); 39.4 (*C*H$_2$-Ph); 54.7, 55.4 (N*C*H-CH$_3$ + *C*H-CH$_2$-Ph); 61.6 (O-CH$_2$-*C*H$_3$); 126.4, 127.6, 128.9, 129.3, 130.1, 130.8, 132.2 (Ar-CH); 136.6 (Ar-C-); 145.4 (N-*C*=N); 162.6 (CH-*C*O-N); 171.3 (*C*OOCH$_2$). Anal. Calcd for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 68.85 ; H, 6.70 ; N, 11.05.

Benzyl (5-(*S*)-Isobutyl-6-oxo-3-phenyl-1,4,5,6-tetrahydro[1,2,4]triazin-1-yl)acetate (10e)

34% yield (Eluent : hexane/ethyl acetate 2/1).White solid, mp : 95-97°C, $[\alpha]_D$ = -38.0° (c=1.5, $CHCl_3$**)**. ^{1}H-NMR (300 MHz, $CDCl_3$,) δ 0.9-1.0 (m, 6H, CH(C*H$_3$*)$_2$); 1.6-1.7 (m, 2H, C*H$_2$*-CH(CH$_3$)$_2$); 1.8-1.9 (m, 1H, CH$_2$-C*H*(CH$_3$)$_2$); 4.1-4.2 (m, 1H, NH-C*H*-CO); 4.57 (s, 2H, N-C*H$_2$*); 5.20 (s, 2H, COOC*H$_2$*-Ph); 5.53 (br s, 1H, N4*H* exchange with D_2O); 7.3-7.4 (m, 8H, Ar-*H*); 7.6-7.65 (m, 2H, Ar-*H*). ^{13}C-NMR (300 MHz, $CDCl_3$) δ 21.7, 23.4 (CH(*C*H$_3$)$_2$); 24.3 (*C*H(CH$_3$)$_2$); 41.6 (*C*H$_2$-CH(CH$_3$)$_2$); 50.4 (NH-*C*H-CO); 51.9 (N-*C*H$_2$); 67.1 (COO*C*H$_2$-Ph); 126.5, 128.4, 128.5, 128.7, 128.8, 130.6, 132.2 (Ar-CH); 135.6 (Ar-

C-); 146 (N-*C*=N); 163.1 (CH-*C*O-N); 168.8 (*C*OOCH$_2$). Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.14 ; H, 6.75 ; N, 10.76.

Ethyl 2-(5-(*S*)-Isobutyl-6-oxo-3-phenyl-1,4,5,6-tetrahydro[1,2,4]triazin-1-yl)-3-phenyl propionate (10f)

Two diastereomers were isolated : 53 % overal yield (Eluent : hexane/ethyl acetate 6/1).

HPLC: R_{t1}=26.4 min (Vydac, gradient H_2O/MeOH: 30 min [98/2 - 0/100], flow 1 mL/min). White solid, mp: 139-141°C (isopropyl ether), $[\alpha]_D$= +57.5° (c=1, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.9-1.1 (m, 6H, CH(C*H*$_3$)$_2$); 1.28 (t, 3H, J=7.1 Hz, OCH$_2$-C*H*$_3$); 1.5-1.8 (m, 3H, C*H*$_2$-C*H*(CH$_3$)$_2$); 3.50 (d, 2H, J= 7.8 Hz, C*H*$_2$-Ph); 3.9-4.0 (m, 1H, N-C*H*-CH$_2$-CH); 4.24 (q, 2H, J=7.1 Hz, OC*H*$_2$); 5.02 (br s, 1H, N4*H* exchange with D_2O); 5.61 (t, 1H, J=7.8 Hz, C*H*-CH$_2$-Ph); 7.1-7.3 (m, 5H, CH$_2$-Ar-*H*); 7.4-7.5 (m, 3H, Ar-H); 7.7-7.8 (m, 2H, Ar-H). ^{13}C-NMR (200 MHz, $CDCl_3$) δ 14.4 (OCH$_2$-*C*H$_3$); 21.9 and 23.4 (CH(*C*H$_3$)$_2$); 24.4 (*C*H(CH$_3$)$_2$); 34.6 (*C*H$_2$-CH(CH$_3$)$_2$); 41.2 (*C*H$_2$-Ph); 51.9 (N-*C*H-CH$_2$-CH); 58.9 (*C*H-CH$_2$-Ph); 61.7 (O*C*H$_2$); 126.7, 127.1, 128.9, 129.4 and 130.8 (Ar-CH); 132.5 and 138.0 (Ar-C-); 145.8 (N-*C*=N-); 163.5 (*C*OOEt); 170.6 (N-*C*O-CH-). MS m/z 408.2 $(M+H)^+$. Anal. Calcd for $C_{24}H_{29}N_3O_3$: C, 70.74; H, 7.17; N, 10.31. Found: C, 70.90 ; H, 7.31 ; N, 10.02.

HPLC: R_{t2}=27.2 min (Vydac, gradient H_2O/MeOH: 30 min [98/2 - 0/100], flow: 1 mL/min). Colorless oil, $[\alpha]_D$= -98.3° (c=1.65, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.8-1.0 (m, 6H, CH(C*H*$_3$)$_2$); 1.1-1.4 (m, 4H, CH$_2$-C*H*(CH$_3$)$_2$ + OCH$_2$-C*H*$_3$); 1.5-1.6 (m, 2H, C*H*$_2$-CH(CH$_3$)$_2$); 3.4-3.5 (m, 2H, C*H*$_2$-Ph); 3.9-4.0 (m, 1H, N-C*H*-CH$_2$-CH); 4.22 (q, 2H, J=7.2 Hz, OC*H*$_2$); 5.02 (br s, 1H, N4*H* exchange with D_2O); 5.5-5.6 (m, 1H, C*H*-CH$_2$-Ph); 7.1-7.3 (m, 5H, CH$_2$-Ar-*H*); 7.4-7.5 (m, 3H, Ar-H); 7.6-7.7 (m, 2H, Ar-H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ 14.4 (OCH$_2$-*C*H$_3$); 21.8 and 23.1 (CH(*C*H$_3$)$_2$); 24.1 (*C*H(CH$_3$)$_2$); 34.7 (*C*H$_2$-CH(CH$_3$)$_2$); 41.5 (*C*H$_2$-Ph); 51.9 (N-*C*H-CH$_2$-CH); 58.7 (*C*H-CH$_2$-Ph); 61.4 (O*C*H$_2$); 126.4, 128.3, 128.8, 129.6 and 130.6 (Ar-CH.); 132.5 and 137.7 (Ar-C-); 145.0 (N-*C*=N-); 162.3 (*C*OOEt); 170.4 (N-*C*O-CH-). Anal. Calcd for $C_{24}H_{29}N_3O_3$: C, 70.74; H, 7.17; N, 10.31. Found: C, 70.99 ; H, 7.21 ; N, 10.20.

Ehtyl 2-(5-(*S*)-Isobutyl-6-oxo-3-phenyl-1,4,5,6-tetrahydro[1,2,4]triazin-1-yl)propionate (10g)

Two diastereomers were isolated : 61 % over all yield (Eluent : hexane/ethyl acetate 5/1).

HPLC: R_{t1}=17.8 min (Vydac, gradient H_2O/MeOH: 30 min [60/40 - 0/100], flow: 1 mL/min). White solid, mp : 114-116°C (EtOH), $[\alpha]_D$= -3.2° (c=0.63, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.9-1.1 (m, 6H, CH(C*H*$_3$)$_2$); 1.24 (t, 3H, J=7.2 Hz, OCH$_2$-C*H*$_3$); 1.61 (d, 3H, J=7.2 Hz, NCH-C*H*$_3$); 1.7-1.9 (m, 3H, C*H*$_2$-C*H*(CH$_3$)$_2$); 4.1-4.3 (m, 3H, N-C*H*-CH$_2$-CH + OC*H*$_2$); 5.06 (br s, 1H, N4*H* exchange with D_2O); 5.34 (q, 1H, J=7.2 Hz, NC*H*-CH$_3$); 7.4-7.5 (m, 3H, Ar-H); 7.6-7.7 (m, 2H, Ar-H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ 14.3 and 14.6 (OCH$_2$-*C*H$_3$ + NCH-*C*H$_3$); 21.8 and 23.4 (CH(*C*H$_3$)$_2$); 24.3 (*C*H(CH$_3$)$_2$); 41.1 (*C*H$_2$-CH(CH$_3$)$_2$); 52.2 (N-*C*H-CH$_2$-CH); 54.0 (N*C*H-CH$_3$); 61.3 (O*C*H$_2$); 126.3, 128.9, and 130.6 (Ar-CH); 132.5 (Ar-C-); 145.2 (N-*C*=N-); 162.7 (*C*OOEt); 171.2 (N-*C*O-CH-). Anal. Calcd for $C_{18}H_{25}N_3O_3$: C, 65.24; H, 7.60; N, 12.68. Found: C, 65.57; H, 7.84 ; N, 12.30.

HPLC: R_{t2}=18.7 min (Vydac, gradient H_2O/MeOH: 30 min [60/40 - 0/100], flow: 1 mL/min). White solid, mp : 67-68°C (EtOH), $[\alpha]_D$= -77.8° (c=0.7, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.0-1.1 (m, 6H, CH(C*H*$_3$)$_2$); 1.25 (t, 3H, J=7.0 Hz, OCH$_2$-C*H*$_3$); 1.60 (d, 3H, J=7.1 Hz, NCH-C*H*$_3$); 1.7-1.9 (m, 3H, C*H*$_2$-C*H*(CH$_3$)$_2$); 4.1-4.3 (m, 3H, N-C*H*-CH$_2$-CH + OC*H*$_2$); 5.13 (br s, 1H, N4*H* exchange with D_2O); 5.28 (q, 1H, J=7.1 Hz, NC*H*-CH$_3$); 7.4-7.5 (m, 3H, Ar-H); 7.6-7.7 (m, 2H, Ar-H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ 14.4 and 14.8 (OCH$_2$-*C*H$_3$ + NCH-*C*H$_3$) ; 21.7 and 23.4 (CH(*C*H$_3$)$_2$); 24.4 (*C*H(CH$_3$)$_2$); 41.4 (*C*H$_2$-CH(CH$_3$)$_2$); 52.0 (N-*C*H-CH$_2$-CH); 54.5 (N*C*H-CH$_3$); 61.3 (O*C*H$_2$); 126.3, 128.9, and 130.7 (Ar-CH.); 132.4 (Ar-C-.); 145.5 (N-*C*=N-); 162.3 (*C*OOEt); 171.1 (N-*C*O-CH-).

5-(*S*)-Benzyl-3-[(*S*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-2-phenethyl]-1-methyl-4,5-dihydro-1,2,4-triazin-6-(1*H*)-one (12)

The title compound was prepared from 4,5-dihydrotriazinone **(1a)** (150 mg, 0.37 mmol), methyl iodide (24 μL, 0.40 mmol) and a dispersion of sodium hydride in mineral oil (w/w 60%, 16 mg, 0.40 mmol) following method C. The residue was chromatographed on silica gel (eluent: hexane/ethyl acetate 2/1) to give a white solid **(13)** (100 mg, 64%), mp : 144-147°C (petrolum ether), $[\alpha]_D$= -69.5° (c=3, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 9H, C(C*H*$_3$)$_3$); 2.6-3.3 (m, 4H, 2x C*H*$_2$-Ph); 3.32 (s, 3H, NC*H*$_3$); 4.1-4.3 (m, 2H, 2x C*H*-CH$_2$); 4.80 (d, 1H, J=7.3 Hz, N4*H* exchange with D_2O); 5.14 (br s, 1H, N*H*Boc exchange with D_2O); 7.0-7.4 (m, 10H, Ar-H.). ^{13}C-NMR (300 MHz, $CDCl_3$) δ 28.6 (C(*C*H$_3$)$_3$); 36.6 (N*C*H$_3$); 38.9 and 40.2 (2x *C*H$_2$-Ph); 54.1 and 55.3 (2x *C*H-CH$_2$); 80.8 (*C*(CH$_3$)$_3$); 127.3, 129.0, and 130.1 (Ar-CH); 136.6 and 137.3 (2Ar-C-); 147.6 (N-*C*=N-); 156.1 (N-*C*OO-); 160.8 (N-*C*O-CH-). Anal. Calcd for $C_{24}H_{30}N_4O_3$: C, 68.22; H, 7.15; N, 13.26. Found: C, 67.95; H, 7.02; N, 13.42.

Ethyl [5-(*S*)-Benzyl-3-[(*S*)-1-[*N*-(*tert*-butoxycarbonyl)amino]-2-phenethyl]-6-oxo-1,4,5,6-tetrahydro-[1,2,4]triazin-1-yl]acetate (13)

The title compound was prepared from 4,5-dihydrotriazinone **(1a)** (150 mg, 0.37 mmol), ethyl 2-bromoacetate (45 μL, 0.44 mmol) and a dispersion of sodium hydride in mineral oil (w/w 60%, 17 mg, 0.44 mmol) following method C. The residue was chromatographed on silica gel (eluent: hexane/ethyl acetate 5/2) to provide a colourless oil **(13)** (90 mg, 50%), $[\alpha]_D$= +27.5° (c=0.4, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.34 (t, 3H, J=7.2 Hz, OCH_2-C*H*$_3$); 1.36 (s, 9H, C(C*H*$_3$)$_3$); 2.87 (AB part of ABX, 2H, J_{AB}=13.4 Hz, J_{AX}= 10.5 Hz, J_{BX}=7.4 Hz, Δδ=0.45, C*H*$_2$-Ph); 2.9-3.4 (m, 2H, C*H*$_2$-Ph); 4.0-4.1 (m, 1H, C*H*-CH_2-Ph); 4.2-4.3 (m, 3H, C*H*-CH_2-Ph + OCH_2-C*H*$_3$); 4.43 (q, 2H, J=16.8 Hz, NC*H*$_2$); 4.76 (d, 1H, J=6.1 Hz, N4*H* exchange with D_2O); 5.03 (br s, 1H, N*H*Boc exchange with D_2O); 7.1-7.4 (m, 10H, Ar-H). ^{13}C-NMR (300 MHz, $CDCl_3$) δ 14.5 (OCH_2-*C*H_3); 28.9 (C(*C*H_3)$_3$); 39.4 and 40.3 (2x *C*H_2-Ph); 50.5 (N*C*H_2-); 53.8 and 55.1 (2x *C*H-CH_2); 61.4 (O*C*H_2); 86.0 (*C*(CH_3)$_3$); 127.4, 129.1, 129.6, 129.9 and 130.1 (Ar-CH); 136.4 and 137.2 (2 Ar-C-); 148.0 (N-*C*=N-); 156.5 (N-*C*OO-); 161.4 (N-*C*O-CH-) ; 168.5 (*C*OOEt). MS m/z 495.25 $(M+23)^+$

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