Tetrahedron 65 (2009) 1995–2004

Contents lists available at ScienceDirect

Tetrahedron

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

Chemoselective asymmetric synthesis of *C*-3a-(3-hydroxypropyl)-tetrahydropyrrolo[2,3-*b*]indole and *C*-4a-(2-aminoethyl)-tetrahydropyrano[2,3-*b*]indole derivatives

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ARTICLE INFO

Article history:
Received 21 October 2008
Received in revised form 3 December 2008
Accepted 5 January 2009
Available online 8 January 2009

ABSTRACT

The asymmetric synthesis of new tetrahydropyrrolo[2,3-*b*]indole **19** and tetrahydropyrano[2,3-*b*]indole **20** rings, substituted in position C-3a and C-4a with a hydroxy- and an amino functionalized chain, respectively, was performed starting from the racemic spiro[cyclohexane-1,3′-indoline]-2′,4-diones **7**. The enantiopure spiro oxo-azepinoindolinone (+)-**10**, obtained from (±)-**7** by the way of an asymmetric ring enlargement, and the amino acid (+)-**14**, obtained by the hydrolysis of **10**, were prepared as key intermediates for the synthesis of enantiopure compounds (−)-**19** and (−)-**20**. Since the amino acid **14** is the common intermediate for the chemoselective preparation of derivatives **19** and **20**, experimental and computational studies were performed in order to selectively obtain these compounds and to provide a mechanistic rationalization for their formation.

1. Introduction

Pyrroloindolines are a subclass of alkaloid structural motifs that commonly exhibit biological activity. The hexahydropyrrolo[2,3-*b*]indole skeleton is characteristic of alkaloids isolated from Calabar bean (*Physostigma venenosum*)[1] as well as from other alkaloids such as those extracted from the skin of Australian myobatrachid frogs of the genus *Pseudophryne*[2] and from marine invertebrates of the phylum *Bryozoa* such as *Flustra foliaceae*.[3] Both pseudophrynamine **1** and flustramine **2** alkaloids have a methyl group at N-1, a prenyl or 'reverse' prenyl chain on C-3a, and in general differ in the substituent on N-8 and on the aromatic ring (Fig. 1).

Pharmacological investigations on compounds **1**[4] and **2**[3a,b,d,5] or on analogous compounds[6] are scarcely documented, probably because of the low availability of the naturally occurring compound. The crucial steps for the formation of the above alkaloids are the functionalization on C-3a with a different chain, the formation of the third pyrroline ring and the orthogonal functionalization of the two nitrogen atoms.

The structural and stereochemical features of these alkaloids make their total synthesis appealing as documented by the literature. Different reagents were used for the preparation of compounds **1** and/or **2** such as tryptamine derivatives,[7] indoleacetic acid derivatives,[8] 1-methoxyindole-3-carbaldehyde,[9] L-tryptophane[10] and oxindole.[11] Other starting materials are the 2-oxofuro[2,3-*b*]indolines,[12] the 2,3-dihydropyrrolo[2,3-*b*]indoline-2-carboxylate derivatives,[13] the 2-allyloxyindolin-3-one,[14] the spirooxindole[15] and alkynylcarbodiimides.[16]

Aside from the hexahydropyrroloindole skeleton, few synthetic examples on the preparation of alkaloids containing the

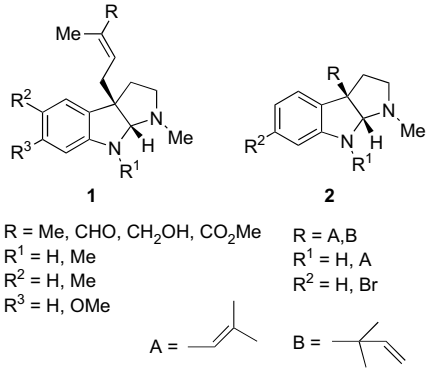

Figure 1. Alkaloids of *Pseudophryne* and *Flustra foliaceae*.

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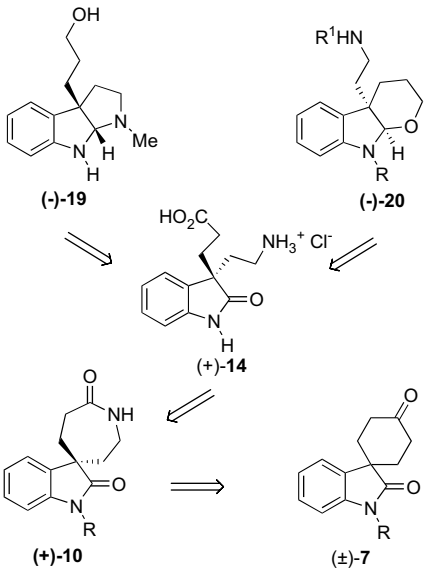
doi:10.1016/j.tet.2009.01.004



Scheme 1. Retrosynthetic analysis of compounds **19** and **20**.

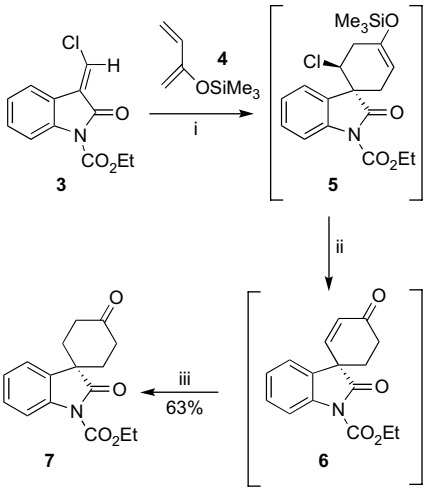
pyranoindole ring have been reported in the literature,[17] even if this skeleton is included in more complex molecules.[18]

Considering the biological interest of the above rings, we planned the asymmetric synthesis of both new hexahydropyrroloindole and pyranoindole derivatives **19** and **20** (Scheme 1) since the polyfunctionalized intermediate **14** was available. In fact, as shown in Scheme 1, the preparation of both hexahydropyrroloindole derivative **19** and tetrahydropyrano[2,3-*b*]indole ring **20** takes advantage of a common intermediate, the new amino acid **14**, which is prepared from the spiro ketone **7**, through the spiroazepinoindoline derivative **10** containing an interesting scaffold of biological importance.[19] Compound **19** is characterized by an orthogonal substitution at nitrogen atoms (i.e., methyl group at N-1, unsubstitution at N-8) and most of all, is substituted on C-3a with a hydroxy functionalized chain which makes this compound a valuable synthon for further transformations. Alternatively, the 2-2,3,4,4a,9,9a-hexahydropyrano[2,3-*b*]indole **20** is functionalized at C-4a with a ethanamine chain.

The asymmetric transformation of racemic **7** in the enantiopure compound (+)-**10** was also realized, thus assuring the preparation of enantiopure compounds (−)-**19** and (−)-**20**. Since the transformation of derivative **14** into **19** or **20** requires different reductive steps, both experimental and computation studies on their chemoselective formation were performed.

2. Results

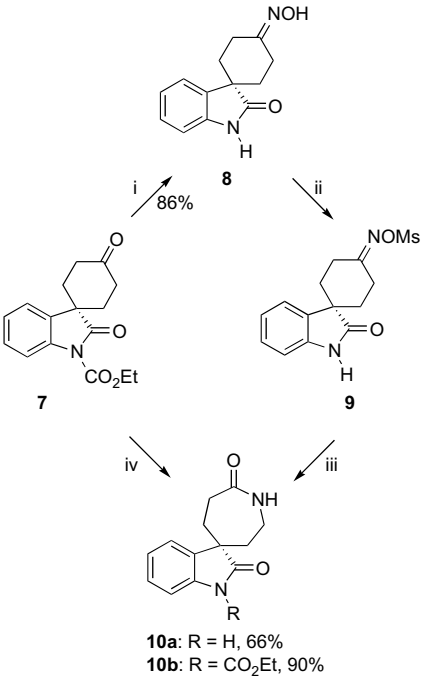
Recently,[20] we reported on a three step synthesis of reagent **7** (55% overall yield) using a Diels–Alder reaction starting from 3-chloromethylene-2-indolone **3** and the Danishefsky's diene. Some disadvantages, related to the formation of by-products deriving from the transformation of the primary cycloadduct into diphenyl compounds, had been encountered using this diene. Furthermore, the difficulty to reproduce the reaction time and the use of the expensive Danishefsky's diene prompted us to revisit this reaction and a different synthetic protocol was planned starting from dienophile **3** and the cheaper 2-trimethylsilyloxybutadiene **4** (Scheme 2). The reaction was performed on a multi-gram scale (24 g), without isolation of the intermediates, by reacting an excess of diene **4** (**3**/**4**, 1:3) in toluene at reflux. After 3 h the spirocyclohexenoneindolone **5** was formed (^{1}H NMR analysis). The crude reaction mixture was treated with triethylamine hydrogen



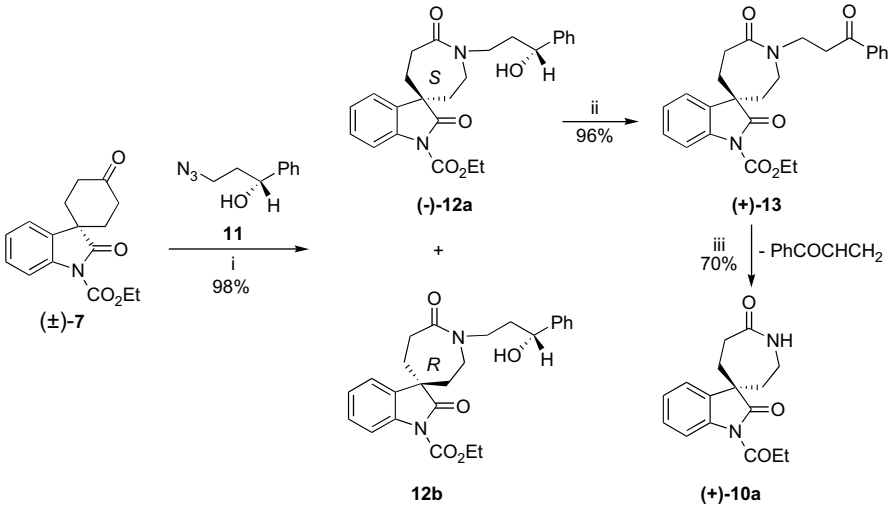
Scheme 2. Synthesis of spiro ketone **7**. Reagents and conditions: (i) toluene, Δ; (ii) $Et_3N{\cdot}HF$, toluene, 25 °C; (iii) H_2, Pd/C, toluene.

fluoride (1 equiv) for 2 h at room temperature to give the unsaturated ketone **6**. Its reduction with hydrogen and Pd/C at room temperature (24 h), afforded pure spiro ketone **7** (63%). The purification of intermediate **6** by column chromatography (65%) was also possible.

Starting from **7**, different synthetic strategies were tested aiming to transform the cyclohexanone ring into the azepinone, the real intermediate for the preparation of amino acid **14**. The reaction of **7** with hydroxylamine (8 equiv) in EtOH/H_2O and sodium acetate at reflux gave oxime **8** (86%) deprotected at the indole nitrogen atom (Scheme 3). Beckmann rearrangement of **8** to **10** was studied under different reaction conditions. The use of strong acids (H_2SO_4, PPA, etc.) gave only tarry compounds. Alternatively, oxime **8** was transformed into the corresponding *O*-mesylate **9** with mesyl chloride at 0 °C in CH_2Cl_2 in the presence of triethylamine (TEA),



Scheme 3. Synthesis of spiro azepinoindole **10**. Reagents and conditions: (i) AcONa, EtOH/H_2O, $NH_2OH{\cdot}HCl$, reflux; (ii) MsCl, TEA, CH_2Cl_2, 0 °C; (iii) **10a**: chromatography on neutral Al_2O_3; (iv) **10b**: H_2SO_4, NaN_3, $CHCl_3$ (from −10 to 25 °C).



Scheme 4. Synthesis of enantiopure compound (+)-**10**. Reagents and conditions: (i) CH_2Cl_2, −80 °C, $BF_3{\cdot}Et_2O$, then 25 °C, then 5% $NaHCO_3$; (ii) PCC, SiO_2, CH_2Cl_2, 25 °C; (iii) NaH, THF, 65 °C.

which allowed the regioselective functionalization of the hydroxy group. The azepinone derivative **10a** (66%) was directly obtained during the chromatographic work-up of compound **9** using neutral alumina (Scheme 3).

An alternative and more efficient protocol to build the azepino ring was found using the modified Schmidt reaction[21] consisting in the reaction of a cooled solution (−10 °C) of ketone **7** in $CHCl_3$ under stirring with H_2SO_4 (11 mmol) followed by addition of sodium azide (4 equiv). Aiming to increase the yield, it is essential to operate in a closed round-bottle flask, to interrupt the stirring after 30 min and to warm the reaction at room temperature (12 h). Pure lactame **10b**, protected at the indole nitrogen atom, was isolated in 90% yield (Scheme 3).

The asymmetric synthesis of enantiopure derivative (+)-**10b** was also planned using the procedure reported by Sahasrabudhe et al.[22] consisting of the reaction of a cyclic ketone with an enantiopure organic azide containing a stereocentre. In our case, *R*-3-azido-1-phenylpropanol (**11**) was made to react with racemic **7** in dichloromethane at −80 °C in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$. The reaction occurred in good diastereoselectivity and compounds (−)-**12a** and **12b** were obtained in 98% yield and 87:13 ratio (HPLC analysis) after hydrolysis (5% $NaHCO_3$) (Scheme 4).

Pure compound (−)-**12a**, obtained by simple crystallization, is characterized by an *S* absolute configuration at the spiro carbon atom, as confirmed by X-ray analysis (Fig. 2). Any attempt to isolate pure stereoisomer **12b** failed.

The deprotection of the nitrogen atom of the azepino ring was first performed by oxidizing the hydroxy group of the chain with PCC in dichloromethane (25 °C, 3.5 h) in presence of SiO_2 to gave the keto derivative (+)-**13** (96%), which was then treated with NaH in THF at 65 °C (3 h). Compound (+)-**10a** was isolated in 70% yield after purification (Scheme 4).

The selective hydrolysis of the lactam function of the azepine ring was performed in aqueous HCl (20%, 100 °C) starting from both (±)-**10b** and (+)-**10a** giving amino acids (±)-**14** and (−)-**14**, respectively, in quantitative yield. Their treatment with EtOH in the presence of $SOCl_2$ gave the corresponding esters (±)-**15** and (−)-**15** (95%) (Scheme 5).

The formation of the hexahydropyrroleindole nucleus was achieved according to the method reported by Somei et al.[9] consisting of the protection of the amino group as carbonate followed by its transformation into the tetrahydropyrroloindole ring by reduction. The amino group was protected using ethyl chlorocarbonate (2 equiv) operating in dichloromethane and in the presence

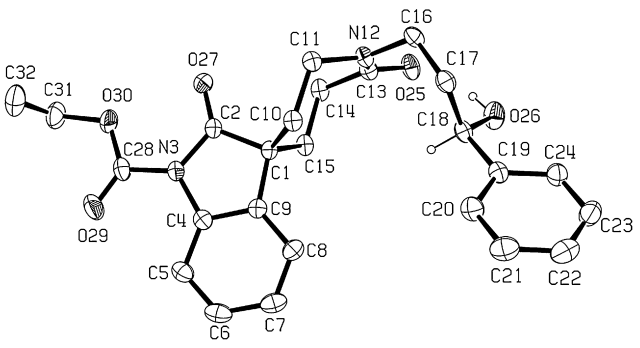
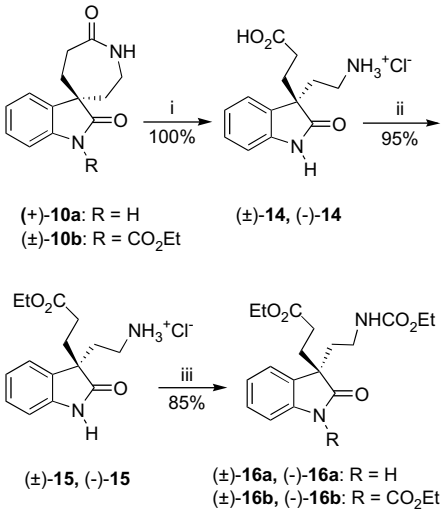


Figure 2. ORTEP plot of compound (−)-**12a** with numbering scheme. ADPs at 20% probability level. For clarity, only H atom bonded to the stereo centre C-18 and of hydroxy group is shown.



Scheme 5. Synthesis of amino acids **14** and derivatives. Reagents and conditions: (i) 20% HCl, 100 °C; (ii) EtOH, $SOCl_2$, reflux; (iii) **16a**: $ClCO_2Et$, (2 equiv), K_2CO_3, CH_2Cl_2, 25 °C; **16b**: $ClCO_2Et$ (4 equiv), TEA, CH_2Cl_2, 25 °C.

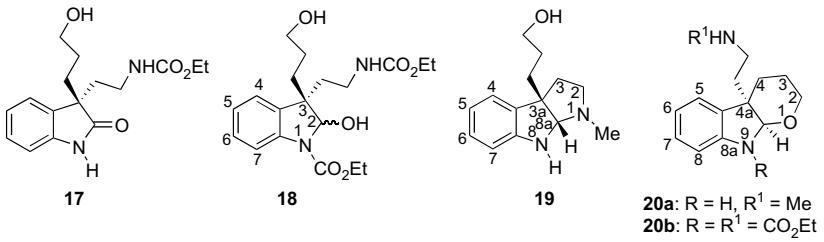


Chart 1. Products of the reduction of compounds **16**.

of an aqueous solution of potassium carbonate. The corresponding protected amino acids (±)-**16a** (75%) and (−)-**16a** (75%) were isolated from (±)-**15** and (−)-**15**, respectively (Scheme 5). It has to be pointed out that the use of TEA as the base gave a mixture of compounds **16a** and **16b**, the last one protected at both amino groups. To achieve the protected compound (−)-**16b** (85%), an excess of ethyl chlorocarbonate (4 equiv) is needed in the presence of TEA starting from (−)-**15** (Scheme 5).

The chemoselective reduction of the functional groups in compounds **16** was studied aiming to obtain both tetrahydropyrrolo[2,3-*b*]indole and tetrahydropyrano[2,3-*b*]indole scaffolds by using selective reactive conditions. Compounds deriving from the partial or total reduction of the different functional groups are shown in Chart 1 and the reaction conditions adopted to reduce reagents **16** are reported in Table 1.

The reduction of (±)-**16a** was performed with $LiAlH_4$ in THF at different temperatures and equivalents of hydride ion. As shown in Table 1, by using the reducing agent (from 4 to 32 equiv, entries 1 and 3) at 25 °C or by heating (4 equiv, entry 2), the selective reduction of the ester function was operative giving the alcohol (±)-**17** in good yield. The goal in the formation of the pyrrole[2,3-*b*]indole ring from (±)-**16a** was achieved by using an excess of $LiAlH_4$ and heating (entry 4). 2,3,8,8a-Tetrahydro-1*H*-pyrrole[2,3-*b*]indole derivative **19**, unprotected at N-8, functionalized at C-3a with the 3-hydroxypropyl chain and at N-1 with a methyl group was isolated in good yield.

Considering that the *N*-alkoxycarbonylamide group is reduced to a hemiaminal function faster then the amide and carbamate functions, we planned the reduction of **16b** with the aim of obtaining the tetrahydropyrano[2,3-*b*]indole ring, via an intermediate such as **18**. In this case too, different reaction conditions were tested (Table 1, entries 5–7) using $LiAlH_4$, which gave mixture of compounds as shown by ^{1}H NMR spectra. Alcohol **17** was the main compound at room temperature by using conditions reported in entries 5 and 6. Pyran derivative **20b** was also obtained when using a strong excess of $LiAlH_4$ (entry 6). Performing the reduction with an excess of $LiAlH_4$ and heating (entry 7), gave compound **19** as the main product. Tetrahydropyrano[2,3-*b*]indole derivative **20a**, functionalized at C-4a with the 2-aminoethyl chain and unprotected at N-9a, was isolated as by-product. To prevent reduction of the ester function before the carbonyl group of the oxindole ring, **16b** was treated both with selectrides and with $NaBH_4$. The use of both K- and L-Selectride is not effective in the formation of compounds like **18** and/or **20** (^{1}H NMR analyses). A mixture of compounds was first obtained by using $NaBH_4$ in a mixture of THF and EtOH, but by controlling the reaction temperature as well as the amount of EtOH, which is necessary to make the reduction operative, our synthetic target was achieved. As reported in entry 8, the use of THF/EtOH (1:1, from 25 °C to reflux) gave **17** as the main compound (50%) together with the *N*-protected compound **18** (mixture of two diastereoisomers) in which both the ester function and the carbonyl group of the oxindole ring were reduced. By decreasing the temperature (from 0 to 25 °C) and the amount of EtOH (entry 9), the hemiaminal **18** was the sole reaction product. Instead, by performing the reaction as reported in entry 10, both intermediate **18** and product **20b** (2:1) were isolated. Interestingly, when the same crude reaction mixture was heated in toluene in presence of *p*-TSA, the complete transformation of **18** into **20b** was observed. The competitive formation of tetrahydropyrroloindole and tetrahydropyranoindole ring, as a mixture of compounds, was reported in the literature.[23]

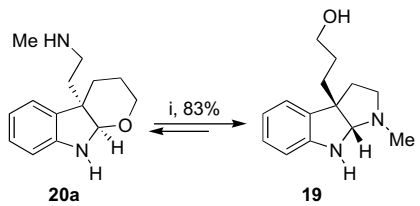
In order to understand if a transformation between **19** and **20** was possible, compound **20a** was treated both with a catalytic amount of a base (TEA in CH_2Cl_2, both at 25 °C and reflux) or an acid. In the first case, the transformation of **20a** into **19** was not observed. Instead, operating at room temperature in the presence of *p*-TSA in CH_2Cl_2 after 16 h a quantitative transformation of **20a** into **19** was operative. It has to be concluded that the tetrahydropyrroloindole derivative **19** is probably the thermodynamic compound and is not in equilibrium with the kinetic compound **20a**. In fact, **19** did not equilibrate to **20a** when standing in CH_2Cl_2 at room temperature in presence of *p*-TSA (Scheme 6).

To confirm our hypothesis, energies of the optimized structures for compounds **19** and **20a** (Fig. 3) were computed at the MP2/6-311+G(3df,2p)//HF-6-31+G(d,p) level in order to verify their thermodynamic stability. As expected, compound **19** was the most

Table 1
Reaction conditions for the reduction of compounds **16**

Entry	Reagent	Reducing agent	Equiv	Solvent (ratio)	*T* (°C)	Reaction time (h)	Products
1	**16a**	$LiAlH_4$	4	THF	25	4	**17** (80%)[a]
2	**16a**	$LiAlH_4$	4	THF	Reflux	6	**17**[b]
3	**16a**	$LiAlH_4$	32	THF	25	12	**17**[b]
4	**16a**	$LiAlH_4$	32	THF	Reflux	12	**19** (79%)[a]
5	**16b**	$LiAlH_4$	4	THF	25	8	**17**[b]
6	**16b**	$LiAlH_4$	32	THF	25	12	**17**/**20b** (2:1)[b]
7	**16b**	$LiAlH_4$	32	THF	Reflux	15	**19**/**20a** (7:1)[a]
8	**16b**	$NaBH_4$	8	THF/EtOH (1:1)	[c]	2	**17**/**18** (3:1)[b]
9	**16b**	$NaBH_4$	8	THF/EtOH (4:1)	From 0 to 25	8	**18** (85%)[a]
10	**16b**	$NaBH_4$	8	THF/EtOH (4:1)	From 0 to reflux	4[d]	**18**/**20b**[a] (2:1)

[a] Isolated compound.
[b] ^{1}H NMR analysis.
[c] From 25 °C to reflux.
[d] See Experimental (Supplementary data).



Scheme 6. Isomerization of pyrano- to pyrroloindole. Reagents and conditions: (i) *p*-TSA, CH_2Cl_2, 25 °C.

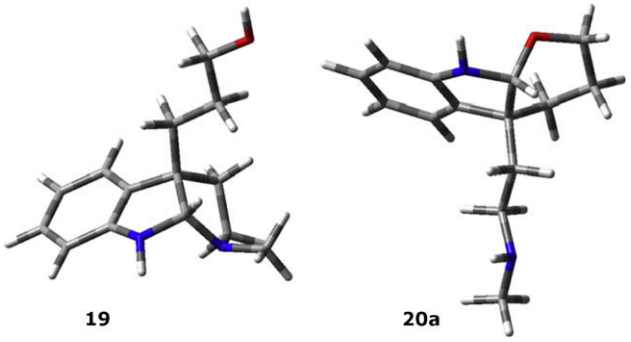
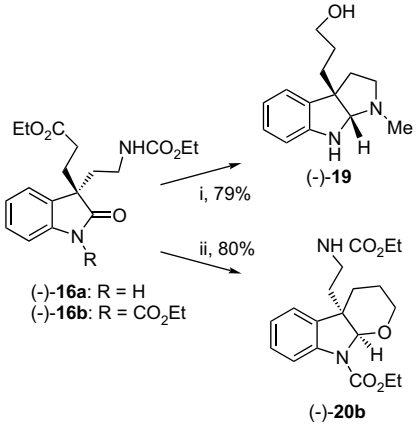


Figure 3. Optimized geometries for compounds **19** and **20a**.



Scheme 7. Preparation of tetrahydropyrroloindole and pyranoindole scaffolds. Reagents and conditions: (i) $LiAlH_4$ (32 mmol), THF, reflux; (ii) $NaBH_4$ (8 mmol), THF/EtOH (4:1), from 0 °C (0.30 h), then 25 °C (1.30 h), then reflux (2 h); then *p*-TSA, toluene, reflux.

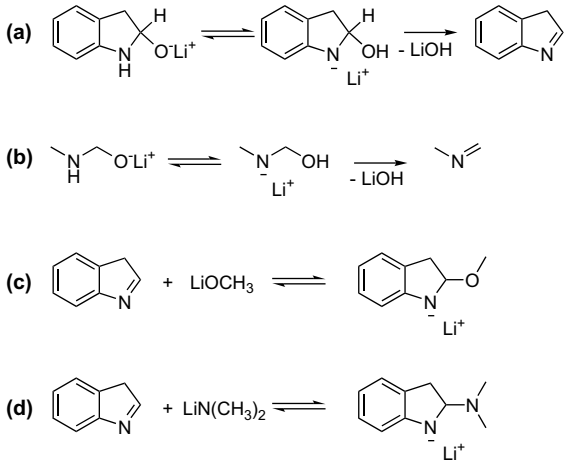
stable ($\Delta G_{\mathbf{19}-\mathbf{20a}}$=−4.1 kcal/mol), confirming the experimental findings.

With the synthetic protocols, which selectively gave the tetrahydropyrroloindole or pyranoindole scaffold, the preparation of enantiopure compounds (−)-**19** and (−)-**20b** was also accomplished. Starting from (−)-**16a**, operating with a large excess of $LiAlH_4$ in THF and by heating, (−)-**19** was isolated in 79% yield (Scheme 7).

Enantiopure derivative (−)-**20b** was obtained from (−)-**16b**, by reduction with $NaBH_4$ in THF/EtOH (4:1) operating at 0 °C (0.30 h) then heating at 25 °C (1.30 h) and then at reflux (2 h). After work-up, the reaction mixture was heated (2 h) in CH_2Cl_2 in presence of *p*-TSA as the catalyst, and compound (−)-**20b** was isolated in 80% yield (Scheme 7).

The data concerning the reduction of compounds **16** suggest that the competitive reduction of the ester function and of the carbonyl of the oxindole balances the formation of the pyran or indoline ring. If the ester was first reduced, sodium ethoxide was formed, which induced the deprotection of nitrogen atom of the oxindole ring of **16b** preventing the reduction of its carbonyl group. Alcohol **17** was generated and then transformed into pyrrole[2,3-*b*]indole derivative **19** by using an excess of $LiAlH_4$ and heating.

The formation of compound **20** must be ascribed to the formation of the corresponding intermediates **18**. If the reduction of the carbonyl function of oxindole to hemiaminal occurred first and then that of the ester function, intermediates **18** are formed, which can cyclize to **20**.



Scheme 8. Theoretically modelled reaction steps.

As confirmed by an independent experiment, **18** was transformed into pyran derivative **20b** by heating in toluene in the presence of *p*-TSA as the catalyst. Instead, the heating of **18** in the absence of a catalyst resulted in the failure of this transformation suggesting that the cyclization occurs via an imine intermediate whose formation is favoured by the presence of the acid.

The basis for the regiochemical cyclization outcome in the reductive process was also clarified by computational studies. A simple but explicative computational model for comparing the two possible cyclizations of compound **16** leading to products **19** and **20a** was adopted. Indeed, a comprehensive reaction model would have been too computationally expensive due to system's dimensions and flexibility, so we thought to study the most representative reaction steps as simplified models. Intermediate **16a** bears three groups that can be reduced by hydrides, namely the side chain ester, the carbamate and the amidic carbonyl of the oxindole moiety. It is known that esters are easily reduced to alcohols, while amides need harder conditions due to the hydroxy group elimination from the hemiaminal intermediate to give an imine, which is then reduced to the amine. Carbamates follow an analogous path, since formamides are reduction intermediates, with the hydroxy group elimination being the rate limiting step. The pyranoindole derivative could reasonably arise from the nucleophilic attack of the alcohol on the imine intermediate, occurring before complete reduction of the side chain carbamate, as competition between *N*-nucleophiles and *O*-nucleophiles should favour the first with the obtainment of the only pyrroloindole derivative. On the other hand, the pyranoindole could lead to the pyrroloindole, thus being an effective reaction intermediate, as soon as the reduction of the carbamate complete and through pyran ring opening and subsequent cyclization. In order to confirm or rebut the above assumptions, theoretical models for the hydroxyl eliminations and alcohol or amine nucleophilic attacks were

Table 2
MP2/6-311+G(3df,2p)//HF/6-31+G(d,p) activation and reaction free energies

Step	$\Delta G^{\ddagger}$ (kcal/mol)	ΔG (kcal/mol)
a	6.7	0.0
b	15.4	7.1
c	1.2	−0.2
c reverse	1.4	0.2
d	−8.1	−23.3
d reverse	15.2	23.3

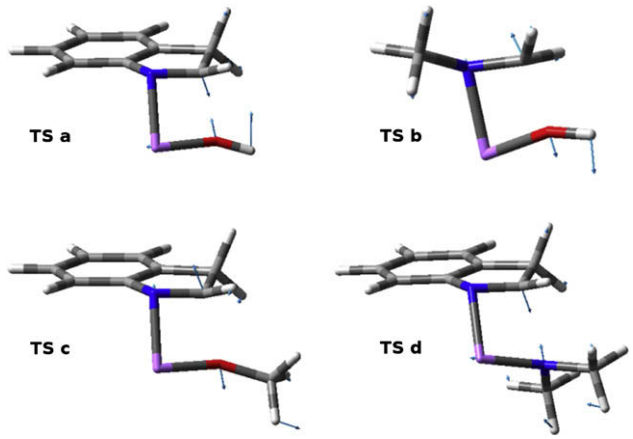


Figure 4. Transition states for the modelled reaction steps. Vectors corresponding to the unique imaginary frequency are represented as blue arrows.

realized as depicted in Scheme 8. Strong basic conditions were simulated and Li^+ was chosen as an approximation of the cationic counterion. Activation and reaction free energies, computed at the MP2/6-311+G(3df,2p)//HF/6-31+G(d,p) level, are reported in Table 2, while optimized geometries for the located transition states **TSa**–**d** are represented in Figure 4.

The hydroxyl elimination from indolin-2-ol (step a) presents an activation barrier of 6.7 kcal/mol and is almost isoergonic, while the corresponding elimination from the aliphatic aminoalcohol (step b, i.e., the intermediate of the reduction of carbamate) has a more than doubled activation barrier (15.4 kcal/mol) and is quite endothermic (7.1 kcal/mol). Those data confirm that the reduction of the oxindole carbonyl is decidedly favoured over the side chain carbamate. It is thus certain that, at an early reaction stage, the only nucleophile able to react with the 3-*H*-indole C-2 is the side chain alcoholic group. The reaction model (step c) for the O-attack presents an activation barrier of only 1.2 kcal/mol and is slightly exothermic, suggesting that the O-cyclization could occur as soon as the cyclic imine is formed, but also that a ring-chain equilibrium is possible due to the low activation barrier of the reverse reaction (1.4 kcal/mol). On the other hand the *N*-attack (step d) occurs barrierless (−8.1 kcal/mol) and is highly exothermic (−23.3 kcal/mol), confirming that the N-cyclization is only limited by the side chain carbamate reduction rate.

Those computational results are in perfect concordance with the experimental outcome of entry 6 (Table 1), where the pyranoindole derivative **20b**, bearing the unreduced carbamate on the side chain, is obtained by operating at room temperature. In conclusion, considering the computational results reported above, it appears reasonable that product **20a** can only be obtained as a by-product in low yields (see entry 7, Table 1) thus justifying the adopted different approaches, which led to derivative **20b**. Finally, it could be argued that both the O- and N-cyclization proceed directly through an intramolecular S_N2 substitution, thus avoiding the cyclic imine intermediate, with the indoline nitrogen or the pyran oxygen behaving as the leaving groups. However, despite many trials, any attempt to localize a S_N2 like transition state for the oxygen or nitrogen attack failed.

The structure of compounds **18b**, **19** and **20a**,**b** was confirmed by analytical and spectroscopic data (see Supplementary data). The ^1H and ^{13}C NMR spectra of compound **19** are in agreement with the structure assigned.[24] The condensation of the two nitrogen containing pentaatomic rings was confirmed by the typical signals at δ=4.48 (C-8a: δ=87.0) associated to H-8a as well as of C-3a at δ=63.1. The singlet at δ=2.44, corresponding to the methyl substituent on N-1 position, confirms the reduction of the carbamate group as well as the signal at δ=3.55 (t, *J* 6.4 Hz, CH_2OH) of the ester function. The NOESY experiment established the cis relationship between H-8a and the C-3a chain. In fact a positive Overhauser effect was observed between H-8a and the signals at δ=3.55 corresponding to the CH_2OH protons.

Pyranoindoline derivatives **20** are characterized by the typical signal of H-9a[17a] that ranges from δ=5.63 (**20a**, C-9a: δ=87.4) to δ=6.06 (**20b**: δ_C=80.8). A singlet at δ=2.76 (δ_C=34.3) revealed the presence of the *N*-Me group in compound **20a**, whose *NH* resonates at low field (δ=11.65) indicating the formation of a hydrogen bond probably with the oxygen of the pyran ring. Our hypothesis is confirmed by the NOESY experiment, which revealed spatial proximity between this proton and both the methyl group and H-9a, thus confirming the cis junction between the two rings. Instead, no information is given regarding the stereochemistry of the ring-junction in **20b**, which is tentatively assigned as cis conformation in agreement with the stereochemistry assigned to **20a**.

In conclusion, the preparation in enantiopure form of the new oxindole amino acid (−)-**14** was performed taking advantage of the asymmetric synthesis of oxo-azepinoindolinone (+)-**10**. Amino acid derivatives **16**, deriving from **14**, are the key intermediates for the chemoselective preparation of the new tetrahydropyrroloindole and pyranoindoline alkaloid scaffolds, functionalized at C-3a with the 3-hydroxypropyl- and at C-4a with the 2-aminoethyl chain, respectively. Our synthetic strategy is very versatile with the possibility of starting from chloromethyleneoxindole differently functionalized on the aromatic ring, to transform the hydroxy chain at C-3a in case of **19** or the amino chain at C-4a in case of compound **20**.

Computational studies on the competitive formation of pyrrolineindole and pyranindole rings were performed from which was evidenced the thermodynamic stability of the first ring and a rationalization of the observed chemoselectivity.

3. Experimental section

3.1. Theoretical calculations

Structures of compounds **19** and **20a** were obtained from a stochastic conformational search conduced at the molecular mechanic level using the MMFF94x forcefield implemented in the MOE software with the default parameters.[25,26] The most stable geometries, as well as reactants, transition states and products of the modelled reaction steps a–d were fully optimized ab initio at the HF/6-31+G(d,p) level, and vibrational frequencies were computed at the same level of theory in order to define optimized geometries as minima (no imaginary frequencies) or transition states (a unique imaginary frequency corresponding to the vibrational stretching of the forming/breaking bonds) and to calculate ZPVE and thermochemical corrections to electronic energies (1 atm, 298.15 K). In order to recover the electron–electron correlation energies, single point calculations were conducted in the gas phase at the MP2/6-311+G(3df,2p) level. All quantum-chemical calculations were performed with the Gaussian03 package.[27]

3.2. General remarks

Reactions were monitored by thin-layer chromatography on 0.25 mm silica gel plates (60 F_{254}) using UV light as a visualizing agent. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with $CHCl_3$ as internal standard, ^1H NMR at 200 or 500 MHz, ^{13}C NMR at 50 or 125 MHz. Infrared spectra were recorded on a Fourier transform IR spectrometer, and values are reported in cm^{-1} units. MAT LCQ ion trap mass spectrometer equipped with a Microsoft Window NT

data system (ESI). Coupling constants (J) are given in hertz. C,H,N analysis on Perkin–Elmer CHN Analyzer Series II 2400.

3.3. Ethyl 2′,4-dioxaspiro[cyclohex-2-en-1,3′-indoline]-1′-carboxylate (±)-6

Operating under a nitrogen atmosphere, oxindole **3** (24 g, 95.7 mmol) was dissolved in anhydrous toluene (500 mL) and the solution was heated at reflux. Diene **4** (50 mL, 287 mmol) was added in portions over a period of 1.5 h. The reaction was monitored by ^{1}H NMR spectroscopy until the disappearance of the signals of the starting oxindole. The crude reaction mixture was cooled and transferred into a polyethylene vessel. TEA·HF (15.6 mL, 99.7 mmol) was added. The mixture was kept stirring at room temperature for 3 h. Unsaturated ketone **6** (17.7 g, 65%) was isolated after column chromatography (cyclohexane/Et_2O, from 10:1 to 10:6). Mp 128 °C (Et_2O), colourless solid; IR (KBr) ν_{max} 1730, 1710, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.97 (d, 1H, J=8.4, H-7′), 7.45–7.36 (m, 1H, Ph), 7.28–7.19 (m, 2H, Ph), 6.50 (d, 1H, J=10.3, H-2), 6.30 (d, 1H, J=10.3, H-3), 4.47 (q, 2H, J=7.0, OCH_2), 3.19–3.02 (m, 1H, H-5), 2.67–2.17 (m, 3H, H-6, H-5), 1.46 (t, 3H, J=7.0, Me); ^{13}C NMR ($CDCl_3$) δ=14.4, 33.0, 33.5, 50.2, 64.0, 115.8, 123.8, 125.5, 129.7, 130.5, 132.2, 138.9, 145.3, 150.9, 174.4, 197.5. MS (ESI) m/z 286.4 (M+H)$^+$. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.34; H, 5.36; N, 4.89.

3.4. Ethyl 2′,4-dioxaspiro[cyclohexane-1,3′-indoline]-1′-carboxylate (±)-7

The crude mixture containing **6** in toluene, prepared as described before, was directly hydrogenated at room temperature for 24 h using Pd/C as the catalyst (10.17 g, 9.566 mmol). The catalyst was filtered over a Celite pad and after column chromatography (cyclohexane/Et_2O, from 10:1 to 10:6) pure keto compound **7** was obtained (17.3 g, 63%). Mp 110 °C (Et_2O); lit.:[20] 110 °C (Et_2O).

3.5. Oxime of spiro[cyclohexane-1,3′-indoline]-2′,4-dione (±)-8

Compound **7** (287.3 mg, 1 mmol) was dissolved in hot EtOH (10 mL). An aqueous solution (2 mL) of NH_2OH·HCl (556 mg, 8 mmol) and AcONa (1.15 g, 14 mmol) was added and the mixture was heated at reflux for 2 h. EtOH was evaporated and the mixture taken up with H_2O (20 mL) and extracted with AcOEt (3×10 mL). The organic layers were dried over Na_2SO_4 and the solvent was removed under vacuum. After crystallization pure oxime **8** (200 mg, 86%) was obtained. Mp 194 °C (Et_2O), colourless solid; IR (KBr) ν_{max} 3360, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=8.37 (br s, 1H, exch., NH), 8.04 (br s, 1H, exch., OH), 7.30–6.91 (m, 4H, Ph), 3.11–2.88 (m, 3H, H-3, H-5), 2.58–2.45 (m, 1H, H-3), 2.18–1.83 (m, 4H, H-2, H-6); ^{13}C NMR ($CDCl_3$) δ=19.7, 26.9, 32.1, 33.3, 46.9, 109.9, 122.5, 123.3, 128.1, 134.3, 139.8, 159.1, 182.0. MS (ESI) m/z 231.2 (M+H)$^+$. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.78; H, 6.15; N, 12.13.

3.6. 1,2,3,5,6,7-Hexahydrospiro[4*H*-azepine-4,3′-3*H*-indol]-7,2′-dione (±)-10a

A solution of oxime **8** (230.3 mg, 1 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled to 0 °C under nitrogen. TEA (0.2 mL, 1.5 mmol in 0.5 mL of CH_2Cl_2) and then MsCl (0.1 mL, 1.4 mmol in 0.5 mL of CH_2Cl_2) were added with stirring at 0 °C. After 1.5 h the organic layer was washed with 5% HCl (5 mL), with a saturated solution of $NaHCO_3$ (5 mL) and then with H_2O (5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under vacuum to give **9**. Crude compound: IR (KBr) ν_{max} 3200, 1704, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=8.11 (s, 1H, exch.), 7.31–6.93 (m, 4H), 3.22 (s, 3H), 3.23–3.06 (m, 2H), 2.68–2.56 (m, 1H), 2.19–1.88 (m, 5H). The crude reaction mixture, containing mesylate (±)-**9** was directly transformed into lactam (±)-**10a** (151.8 mg, 66%) by chromatography on neutral Al_2O_3 (CH_2Cl_2/MeOH, 1:0 to 20:1). Mp 125 °C (CH_2Cl_2/Et_2O), colourless solid; IR (KBr) ν_{max} 3182, 1638 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=8.71 (br s, 1H, exch., NH), 7.29–6.93 (m, 4H, Ph), 6.66 (t, J=5.1, 1H, exch., NH), 4.35–4.19 (m, 1H, H-2), 3.69–3.55 (m, 1H, H-6), 3.28–3.13 (m, 1H, H-2), 2.51–2.40 (m, 1H, H-6), 2.07–1.95 (m, 4H, H-3, H-5); ^{13}C NMR ($CDCl_3$) δ=30.4, 30.5, 36.6 (2C), 47.9, 110.2, 122.6, 122.9, 128.3, 134.9, 139.7, 179.3, 182.5. MS (ESI) m/z 253.2 (M+Na)$^+$. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.84; H, 6.11; N, 12.21.

3.7. Ethyl 7,2′-dioxa-1,2,3,5,6,7-hexahydrospiro[4*H*-azepine-4,3′-3*H*-indole]-1′-carboxylate (±)-10b

To a cooled solution (−10 °C) of **7** (9 g, 31.35 mmol) in $CHCl_3$ (130 mL), concentrated H_2SO_4 (18.8 mL, 344.9 mmol) was added with stirring. Sodium azide (8.6 g, 132.4 mmol) was added over a 15–20 min period. After stirring for 15 min, the reaction mixture was allowed to stand overnight at room temperature. Crushed ice was added to the mixture, which was then treated with 2 M NaOH until pH 6. The crude reaction mixture was extracted with $CHCl_3$ (3×50 mL). The organic layers were dried over Na_2SO_4 and, after evaporation of the solvent, the azepino compound (±)-**10b** (8.54 g, 90%) was obtained. Mp 118 °C (CH_2Cl_2/Et_2O), colourless solid; IR (KBR) ν_{max} 3435, 1780, 1668 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.89 (d, J=8.0, 1H, H-7′), 7.34–7.19 (m, 3H, Ph), 6.23 (br s, 1H, exch., NH), 4.49 (q, J=7.3, 2H, OCH_2), 4.21–4.38 (m, 1H, H-2), 3.66–3.53 (m, 1H, H-6), 3.16–3.09 (m, 1H, H-2), 2.44–2.33 (m, 1H, H-6), 2.13–1.96 (m, 4H, H-3, H-5), 1.47 (t, J=7.3, 3H, Me); ^{13}C NMR ($CDCl_3$) δ=14.47, 30.51, 31.58, 36.66, 37.59, 47.63, 63.82, 115.42, 122.69, 125.33, 128.81, 133.47, 137.80, 151.07, 177.83, 178.81. (ESI) m/z 325.2 (M+Na)$^+$. Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.58; H, 6.01; N, 9.10.

3.8. Ethyl 7,2′-dioxa-1,2,3,5,6,7-hexahydrospiro[1-(3-hydroxy-3-phenyl-propyl)-4*H*-azepine-4,3′-3*H*-indole]-1′-carboxylates (12)

A solution of (*R*)-3-azido-1-phenylpropanol **11** (924 mg, 5.22 mmol) and spirocyclohexanone (±)-**7** (1 g, 3.48 mmol) in CH_2Cl_2 (60 mL) was cooled to −80 °C. BF_3·OEt_2 (1.32 mL, 10.4 mmol) was added dropwise. The reaction was gradually warmed to room temperature over a period of 48 h. CH_2Cl_2 (20 mL) and an aqueous solution of $NaHCO_3$ (5%, 60 mL) were added and the mixture was stirred at room temperature. After 18 h the layers were separated and the aqueous one was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with NH_4Cl (10 mL), dried over $MgSO_4$ and the solvent was removed under vacuum. A mixture of diastereoisomers **12a**/**12b** (1.65 g, 98%) was obtained. HPLC analysis of the crude reaction mixture showed an 83:13 ratio of diastereomeric lactams (Hypersil column, 5 μ, 250×4.6 mm, CH_2Cl_2/*i*PrOH 95:5, 1.2 mL/min). Pure diastereoisomer (−)-**12a** (1.2 g, 71%) was obtained by crystallization from Et_2O. Compound (−)-**12a**: mp 128 °C, colourless solid; $[\alpha]_D$ −12 (*c* 0.01, $CHCl_3$); IR (KBr) ν_{max} 2924, 1783 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.91 (d, J=8.1, 1H, H-7′), 7.43–7.17 (m, 8H, Ph), 4.76 (dd, J=9.4, 3.4, 1H, *CH*Ph), 4.56 (dd, J=14.7, 5.4, 1H, H-2), 4.51 (q, J=7.1, 2H, OCH_2), 4.06–4.00 (m, 1H+1H exch., *CH*N, OH), 3.59–3.57 (m, 1H, H-6), 3.34 (dt, J=9.1, 4.8, 1H, *CH*N), 3.20 (dd, J=14.7, 4.1, 1H, H-2), 2.50–2.43 (m, 1H, H-6), 2.10–1.87 (m, 6H, H-3, H-5, CH_2CHOH), 1.49 (t, J=7.1, 3H, Me); ^{13}C NMR ($CDCl_3$) δ=14.6, 31.3, 32.2, 37.1, 38.2, 44.5, 46.1, 47.2, 64.1, 70.8, 115.7, 122.7, 125.6, 125.9 (2C), 127.7, 128.9 (2C), 129.2, 133.3, 138.1, 144.4, 151.2, 176.8, 178.0. (ESI) m/z 459.5 (M+Na)$^+$. Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C,

68.75; H, 6.50; N, 6.39. Compound **12b** (mixture with **12a**): ^{13}C NMR ($CDCl_3$) δ=14.6, 31.2, 32.0, 36.0, 37.9, 43.5, 45.4, 47.2, 64.1, 70.3, 115.7, 122.9, 125.6 (2C), 126.0, 127.6, 128.8 (2C), 128.9, 133.3, 138.1, 144.3, 151.2, 177.1, 178.1.

3.9. Ethyl 7,2′-dioxa-1,2,3,5,6,7-hexahydrospiro[1-(3-oxa-3-phenyl-propyl)-4*H*-azepine-4,3′-3*H*-indole]-1′-carboxylates (+)-13

Compound (−)-**12a** (570 mg, 1.3 mmol) was dissolved in CH_2Cl_2 (10 mL). PCC (565 mg, 2.6 mmol) and silica gel (1 g) were added under stirring. After 3.5 h (TLC: cyclohexane/EtOAc, 1:1) the crude reaction mixture was concentrated under vacuum. Column chromatography on silica gel was performed (cyclohexane/EtOAc, 1:1) giving pure (+)-**13** (540 mg, 96% yield). Mp 115 °C (Et_2O), colourless solid; $[\alpha]_D$ +16 (*c* 0.01, $CHCl_3$); IR (KBr) ν_{max} 2924, 1783 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=8.01 (d, *J*=7.1, 2H, Ph), 7.89 (d, *J*=8.1, 1H, Ph), 7.64–7.59 (m, 1H, Ph), 7.53–7.48 (m, 2H, Ph), 7.36–7.30 (m, 1H, Ph), 7.18 (dt, *J*=7.5, 0.7, 1H, Ph), 7.07 (dd, *J*=6.7, 0.8, 1H, Ph), 4.59–4.55 (m, 1H, H-2), 4.53 (q, *J*=7.1, 2H, O*CH*$_2$), 3.96 (ddd, *J*=13.3, 6.8, 6.5, 1H, *CH*N), 3.79 (ddd, *J*=13.3, 6.8, 6.5, 1H, *CH*N), 3.66–3.56 (m, 1H, H-6), 3.51–3.20 (m, 3H, *CH*$_2$COPh, H-2), 2.50–2.40 (m, 1H, H-6), 2.05–1.88 (m, 4H, H-3, H-5), 1.48 (t, *J*=7.1, 3H, Me); ^{13}C NMR ($CDCl_3$) δ=14.6, 31.5, 32.0, 36.8, 38.0, 45.3, 45.7, 47.2, 64.0, 115.5, 122.8, 125.5, 128.6 (2C), 129.0 (2C), 129.1, 133.5, 133.8, 137.2, 138.0, 151.2, 175.8, 178.1, 199.5. (ESI) *m*/*z* 457.4 (M+Na)$^+$. Anal. Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.07; H, 6.06; N, 6.43.

3.10. 1,2,3,5,6,7-Hexahydrospiro[4*H*-azepine-4,3′-(3*H*)-indol]-7,2′-diones (+)-10a

NaH (60%, 1 g, 25 mmol,) was suspended in anhydrous THF (30 mL) under nitrogen. Compound (+)-**13** (520 mg, 1.19 mmol) dissolved in anhydrous THF (15 mL) was added to the mixture, which was heated at 65 °C under stirring for 3 h (TLC: cyclohexane/EtOAc, 1:1). The solid was filtered, the solvent was removed under vacuum and the crude reaction mixture was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 50:1) giving pure (+)-**10a** (250 mg, 70%). Mp 128 °C (CH_2Cl_2/Et_2O) colourless solid; $[\alpha]_D$ +27 (*c* 0.01, MeOH).

3.11. 3-[3-(2-Aminoethyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-propionic acid hydrochloride (14)

Operating in a sealed tube, lactam (+)-**10a** (230 mg, 1 mmol) or (±)-**10b** (302 mg, 1 mmol) was suspended in HCl (3 mL, 20%). The mixture was heated at 100 °C for 12 h. The water was removed obtaining compound (−)-**14** or (±)-**14** in quantitative yield (284 mg). Mp 221–225 °C (acetone), colourless; $[\alpha]_D$ −25 (*c* 0.80, H_2O); IR (KBr) ν_{max} 3500–3000, 1690, 1610 cm^{-1}; ^{1}H NMR (D_2O) δ=7.29–6.94 (m, 4H, Ph), 2.70–2.34 (m, 2H, *CH*$_2$NH$_3^+$), 2.24–1.70 (m, 6H, *CH*$_2$*CH*$_2$CO$_2$H, *CH*$_2$CH$_2$NH$_3^+$); ^{13}C NMR (D_2O) δ=28.8, 31.8, 33.9, 35.3, 51.5, 111.1, 123.7, 124.0, 129.4, 129.6, 141.0, 177.1, 182.3. Anal. Calcd for $C_{13}H_{17}ClN_2O_3$: C, 54.84; H, 6.02; N, 9.84. Found: C, 54.86; H, 6.04; N, 9.82.

3.12. Ethyl 3-[3-(2-aminoethyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-propionate hydrochloride (15)

Amino acid (−)-**14** or (±)-**14** (284.7 mg, 1 mmol) was suspended in EtOH (10 mL) and $SOCl_2$ (1 mL) was added. The mixture was heated at reflux for 5 h under stirring. After solvent evaporation the product was crystallized giving pure (−)-**15** or (±)-**15** (296 mg, 95%). Mp 195 °C (acetone), colourless solid; $[\alpha]_D$ −15 (*c* 0.70, MeOH); IR (KBr) ν_{max} 3600–2700, 1692, 1610 cm^{-1}; ^{1}H NMR (CD_3OD) δ 7.33–6.98 (m, 4H, Ph), 3.93 (q, *J*=7.0, 2H, O*CH*$_2$), 2.70–2.52 (m, 2H, *CH*$_2$NH$_3^+$), 2.24–1.84 (m, 6H, *CH*$_2$*CH*$_2$CO$_2$Et, *CH*$_2$CH$_2$NH$_3^+$), 1.12 (t, *J*=7.0, 3H, Me); ^{13}C NMR (CD_3OD) δ 13.3, 28.9, 32.1, 34.2, 35.6, 50.9, 60.6, 110.4, 122.9, 123.5, 128.9, 130.1, 141.9, 172.9, 180.8. Anal. Calcd for $C_{15}H_{21}ClN_2O_3$: C, 57.60; H, 6.77; N, 8.96. Found: C, 57.56; H, 6.80; N, 8.94.

3.13. Synthesis of compounds 16

Method A. Compound (−)-**15** or (±)-**15** (312.8 mg, 1 mmol) was suspended in CH_2Cl_2 (10 mL). Operating at 25 °C a solution of K_2CO_3 (414 mg, 3 mmol) in H_2O (2 mL) was added with vigorous stirring. A solution of $ClCO_2Et$ (187 μL, 2 mmol) in CH_2Cl_2 (1 mL) was dropped. The stirring was continued for 2 h. The layers were separated and the water one was extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with H_2O (10 mL) and then with brine (10 mL). After drying over Na_2SO4, the crude reaction mixture was chromatographed on silica gel (cyclohexane/AcOEt=1:1). Pure compound (−)-**16a** or (±)-**16a** (261 mg, 75%) was obtained as an oil. *Method B*. Compound (−)-**15** (312.8 mg, 1 mmol) was suspended in dry CH_2Cl_2 (10 mL). The solution was cooled at 0 °C and $ClCO_2Et$ (561 μL, 4 mmol) was added. TEA (739 μL, 5 mmol) was dropped under stirring. The stirring was continued for 6 h at room temperature. A solution of HCl (10%, 10 mL) was added and the layers were separated and the aqueous was extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with HCl (10%, 2×10 mL) and then with H_2O (10 mL). After drying over Na_2SO_4, the crude reaction mixture was purified by column chromatography on silica gel (*n*-pentane/Et_2O, 1:0 to 0:1) obtaining pure compound (−)-**16b** or (±)-**16b** (300 mg, 85%).

3.13.1. Ethyl 3-[3-(2-ethoxycarbonylaminoethyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-propionate (−)-*16a*

Oil; $[\alpha]_D$ −12 (*c* 0.60, $CHCl_3$); IR (KBr) ν_{max} 2929, 1730, 1612 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=8.46 (br s, 1H, exch., NH), 7.28–6.90 (m, 4H, Ph), 4.78 (br s, 1H, exch., NH), 4.09–3.95 (m, 4H, O*CH*$_2$), 3.06–2.91 (m, 2H, *CH*$_2$NH), 2.28–1.71 (m, 6H, *CH*$_2$*CH*$_2$CO$_2$Et, *CH*$_2$CH$_2$NH), 1.16 (t, *J*=7.0, 6H, Me); ^{13}C NMR ($CDCl_3$) δ=14.5, 14.9, 29.4, 33.1, 37.4, 37.6, 51.5, 60.1, 61.1, 110.4, 123.4, 123.9, 128.8, 131.1, 141.2, 156.7, 173.0, 181.6. (ESI) *m*/*z* 349.1 (M+H)$^+$. Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 62.01; H, 6.97; N, 8.02. A second tautomer is present as evidenced in ^{1}H NMR spectrum (δ=9.5, br, exch.; 5.50, br s, exch.).

3.13.2. Ethyl 3-[3-(2-ethoxycarbonylaminoethyl)-1-ethoxycarbonyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-propionate (−)-*16b*

Mp 93 °C (Et_2O), colourless; $[\alpha]_D$ −27 (*c* 0.60, $CHCl_3$); IR (KBr) ν_{max} 2934, 1733, 1608 cm^{-1}; ^{1}H NMR δ=($CDCl_3$) 7.87 (d, *J*=8.1, 1H, H-7), 7.37–7.19 (m, 3H, Ph), 4.58 (t, *J*=5.5, 1H, exch., NH), 4.45 (q, *J*=7.0, 2H, O*CH*$_2$), 3.95 (q, *J*=7.0, 4H, O*CH*$_2$), 2.90–2.83 (m, 2H, *CH*$_2$NH), 2.30–1.80 (m, 6H, *CH*$_2$*CH*$_2$CO$_2$Et, *CH*$_2$CH$_2$NH), 1.46 (t, *J*=7.0, 3H), 1.12 (t, *J*=7.0, 6H); ^{13}C NMR ($CDCl_3$) δ=14.1, 14.2, 14.6, 29.0, 33.8, 37.0, 38.2, 51.1, 60.6, 60.9, 63.6, 115.4, 123.0, 125.3, 129.0, 129.2, 139.5, 150.7, 156.3, 172.3, 177.7. Anal. Calcd for $C_{21}H_{28}N_2O_7$: C, 59.99; H, 6.71; N, 6.66. Found: C, 59.95; H, 6.76; N, 6.60.

3.14. General procedures for the reduction of 16b

Method A. Operating under nitrogen and stirring, $LiAlH_4$ (238 mg, 6.4 mmol) was suspended in dry THF (15 mL). Compound (±)-**16b** (351 mg, 0.8 mmol) dissolved in anhydrous THF (15 mL) was added and the solution was heated at reflux for 15 h. A saturated solution of NH_4Cl was added until no more gas was formed. The mixture was extracted with AcOEt (3×10 mL). After drying over Na_2SO_4, the solvent was removed under vacuum. After column chromatography (CH_2Cl_2/MeOH, 10:1), compounds

19 (126 mg, 68%) and **20a** (20 mg, 10%) were isolated. *Method B*. Compound (±)-**16b** (150 mg, 0.34 mmol) was dissolved in THF (8 mL) and the solution was cooled to 0 °C. A suspension of $NaBH_4$ (26 mg, 0.68 mmol) in EtOH (1.5 mL) was dropped. The mixture was left under stirring for 30 min at 0 °C. The temperature was raised to 25 °C and then the mixture was heated at reflux for 2 h. The solvent was removed under vacuum, EtOAc (10 mL) and water (8 mL) were added to the residue. The layers were separated, the organic one was dried over Na_2SO_4 and the solvent was removed under vacuum. After column chromatography (CH_2Cl_2/MeOH, from 10:0 to 10:1) compounds (±)-**18** (100 mg, 40%), (±)-**20b** (55 mg, 20%) were obtained. *Method C*. Operating under nitrogen and stirring, $LiAlH_4$ (30 mg, 0.8 mmol) was suspended in dry THF (15 mL). Compound (±)-**16a** (278.4 mg, 0.8 mmol) or (±)-**16b** (351 mg, 0.8 mmol) dissolved in anhydrous THF (15 mL) was added and the solution was stirred at room temperature for 4 h. A saturated solution of NH_4Cl was dropped until no more gas was formed. The mixture was extracted with AcOEt (3×10 mL). After drying over Na_2SO_4, the solvent was removed under vacuum obtaining pure compound (±)-**17** (**16a**: 196 mg, 80%; **16b**: 182 mg, 75%). *Method D*. Operating as described for the preparation of **17**, starting from (−)-**16a** and using an excess of $LiAlH_4$ (238 mg, 6.4 mmol) at reflux for 4 h, compound (−)-**19** (146 mg, 79%) was obtained as an oil. *Method E*. Compound **16b** (150 mg, 0.34 mmol) was dissolved in THF (8 mL) and the solution was cooled to 0 °C. A suspension of $NaBH_4$ (26 mg, 0.68 mmol) in EtOH (1.5 mL) was added. The mixture was left under stirring for 30 min at 0 °C and then was warmed to room temperature. After 7.3 h the solvent was removed under vacuum, EtOAc (10 mL) and water (8 mL) were added to the residue. The layers were separated, the organic one was dried over Na_2SO_4 and the solvent was removed under vacuum. After column chromatography (CH_2Cl_2/MeOH, from 10:0 to 10:1) compound (±)-**18** (210 mg, 85%) was isolated from (±)-**16b**. Crude compound, mixture of two diastereoisomers. *Method F*. Starting from (−)-**16b** (150 mg, 0.34 mmol) operating as described before, compound (−)-**18** was obtained. The crude reaction mixture was dissolved in toluene (15 mL) and a catalytic amount of *p*-TSA was added. The mixture was stirred at reflux for 2 h. A solution of NaOH (2 M, 15 mL) was added and the organic layer was separated. After drying over Na_2SO_4, the solvent was removed affording pure compound (−)-**20b** (230 mg, 80%) as an oil.

*3.14.1. 3-[3-(2-Ethoxycarbonylaminoethyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-propan-1-ol (±)-(**17**)*

Mp 135 °C (Et_2O), colourless; IR (KBr) ν_{max} 2933, 1713, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.71 (br s, 1H, exch., NH), 7.27–6.90 (m, 4H, Ph), 4.78 (br s, 1H, exch., NH), 4.02 (q, *J*=7.0, 2H, O*CH*$_2$), 3.48 (t, *J*=7.0, 2H, *CH*$_2$OH), 3.05–2.80 (m, 2H, *CH*$_2$NH), 2.40–1.30 (m, 6H+1H exch., *CH*$_2$CH$_2$NH, *CH*$_2$*CH*$_2$CH$_2$O*H*), 1.18 (t, *J*=7.0, 3H, Me); ^{13}C NMR ($CDCl_3$) δ=15.0, 25.9, 30.2, 34.6, 37.8, 52.0, 61.1, 62.8, 110.3, 123.3, 123.6, 129.2, 132.1, 141.1, 156.8, 182.1. (ESI) *m*/*z* 329.6 $(M+Na)^+$. Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.70; H, 7.27; N, 9.11. A second isomer is present as evicted both in ^1H NMR (δ=9.15, br, exch.; 5.05, br s, exch.) and ^{13}C NMR (δ=30.1, 37.4, 63.2) spectra.

*3.14.2. 3-[3-(2-Ethoxycarbonylaminoethyl)-1-ethoxycarbonyl-2-hydroxy-2,3-dihydro-1H-indol-3-yl]-propan-1-ol (**18**)*

IR (KBr) ν_{max} 3500–3300, 1687, 1647 cm^{-1}. Main isomer: ^1H NMR ($CDCl_3$) δ=7.26–7.06 (m, 4H, Ph), 5.62 (s, 1H, H-2), 4.57 (br s, 1H, exch., NH), 4.39 (q, *J*=6.9, 2H, O*CH*$_2$), 4.13–4.07 (m, 2H, O*CH*$_2$), 3.75–3.62 (m, 2H *CH*$_2$OH), 3.22–3.12 (br s, 1H, *CH*NH), 3.12–3.00 (br s, 1H, *CH*NH), 1.98–1.67 (m, 4H, *CH*$_2$CH$_2$NH, *CH*$_2$CH$_2$OH), 1.60 (br s, 2H, exch., OH), 1.45–1.42 (m, 5H, *CH*$_2$CH$_2$CH$_2$OH, Me), 1.26 (t, *J*=7.1, 3H, Me); ^{13}C NMR ($CDCl_3$) δ=13.9 (×2), 27.4, 29.0, 35.8, 37.0, 44.9, 48.3, 60.1, 61.6, 62.3, 89.4, 114.1, 122.4, 122.9, 127.6, 134.4, 138.8, 155.9. Minor isomer, significative signals: ^1H NMR δ 5.59 (s, 1H), 5.00 (br s, 1H, exch.), 3.62–3.50 (m, 2H; ^{13}C NMR δ=62.1), 3.45–3.22 (m, 2H). Trace amount of other conformers is present in the NMR spectra. (ESI) *m*/*z* 403.3 $(M+Na)^+$. Anal. Calcd for $C_{19}H_{28}N_2O_6$: C, 59.98; H, 7.42; N, 7.36. Found: C, 59.93; H, 7.48; N, 7.31.

*3.14.3. 3-(1-Methyl-2,3,8,8a-tetrahydro-1H-pyrrolo[2,3-b]indol-3a-yl)-propan-1-ol (−)-(**19**)*

$[\alpha]_D$ −59 (*c* 0.80, $CHCl_3$); IR (KBr) ν_{max} 2852, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.05–7.01 (m, 2H, Ph), 6.76–6.71 (m, 1H, Ph), 6.59 (d, *J*=7.8, 1H, Ph), 4.48 (s, 1H, H-8a), 3.87 (br s, 1H, exch., OH), 3.55 (t, *J*=6.4, 2H, *CH*$_2$OH), 2.70–2.67 (m, 1H, H-2), 2.67–2.58 (m, 1H, H-2), 2.44 (s, 3H, Me), 2.08–1.99 (m, 2H, H-3), 1.99–1.78 (m, 2H, *CH*$_2$CH$_2$OH), 1.65–1.35 (m, 3H, *CH*$_2$CH$_2$, CH$_2$OH, NH); ^{13}C NMR ($CDCl_3$) δ=29.2, 36.4, 37.0, 39.9, 52.5, 57.9, 63.1, 87.0, 109.5, 119.4, 123.6, 128.1, 134.9, 150.5. (ESI) *m*/*z* 233.2 $(M+H)^+$. Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.35; H, 8.71; N, 12.05.

*3.14.4. 2-(2,3,4,4a,9,9a-Hexahydropyrano[2,3-b]indol-4a-yl)-N-methylethanamine (**20a**)*

Oil; IR (KBr) ν_{max} 3500–3300, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ=11.65 (br s, 1H, exch., *NH*Me), 7.15 (t, *J*=7.3, 1H, Ph), 7.07 (d, *J*=7.2, 1H, Ph), 6.89 (t, *J*=7.3, 1H, Ph), 6.78 (d, *J*=7.8, 1H, Ph), 5.68 (s, 1H, exch., NH), 5.63 (s, 1H, H-9a), 3.58–3.39 (m, 3H, H-2, *CH*NH), 2.81 (d, *J*=4.4, 3H, Me), 2.66–2.52 (m, 2H, *CHCH*NH), 2.30–2.14 (m, 2H, H-4, *CH*CHNH), 2.06–1.92 (m, 1H, H-4), 1.56–1.27 (m, 2H, H-3); ^{13}C NMR ($CDCl_3$) δ=28.7, 34.6, 35.3, 38.3, 52.5, 58.3, 62.1, 87.0, 110.5, 120.8, 123.3, 129.2, 132.1, 149.3. (ESI) *m*/*z* 233.1 $(M+H)^+$. Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.00; H, 8.80; N, 11.95.

*3.14.5. Ethyl 4a-(2-N-ethoxycarbonylethanamine)-2-(2,3,4,4a,9,9a-hexahydropyrano[2,3-b]indole)-9-carboxylate (−)-(**20b**)*

$[\alpha]_D$ −40 (*c* 0.80, $CHCl_3$); IR (KBr) ν_{max} 3500–3300, 2925, 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ=7.70 (d, *J*=6.8, 1H, H-7), 7.29–7.05 (m, 4H, Ph), 6.06 (s, 1H, H-9a), 4.41–4.27 (m, 2H, O*CH*$_2$), 4.18 (q, *J*=7.2, 2H, O*CH*$_2$), 3.99 (dd, *J*=6.5, 6.4, 1H, *CH*N), 3.84 (dd, *J*=11.0, 7.6, 1H, H-2), 3.58 (dd, *J*=6.4, 6.3, 1H, H-2), 2.92 (ddd, *J*=11.3, 6.2, 5.4, 1H, *CH*N), 2.17 (dd, *J*=12.2, 5.4, 1H, *CH*CH$_2$N), 2.03 (dd, *J*=12.2, 7.6, 1H, *CH*CH$_2$N), 1.97–1.77 (m, 2H, H-4), 1.70–1.50 (m, 1H, H-3), 1.38 (t, *J*=7.1, 3H, Me), 1.34–1.12 (m, 4H, H-3, Me); ^{13}C NMR ($CDCl_3$) δ=14.9, 15.0, 28.6, 35.3, 37.2, 46.2, 54.2, 61.7, 62.3, 63.2, 80.8, 116.9, 123.3, 124.0, 126.3, 128.8, 129.1, 153.9, 155.1. (ESI) *m*/*z* 385.3 $(M+Na)^+$. Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found: C, 62.93; H, 7.27; N, 7.70.

3.15. Isomerization of 20a to 19

Compound **20a** (10 mg, 0.04 mmol) was dissolved in dry CH_2Cl_2 (1 mL) and a catalytic amount of *p*-TSA was added. The mixture was stirred at room temperature. After 16 h a solution of NaOH (0.5 mL, 25%) was added. The layers were separated and the aqueous one was extracted with CH_2Cl_2 (2×2 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated giving compound **19** as an oil (8 mg, 83%).

3.16. Transformation of 18 into 20b

Compound **18** (20 mg, 0.05 mmol) was dissolved in toluene (0.5 mL) and a catalytic amount of *p*-TSA was added. The mixture was stirred at reflux for 2 h. A solution of NaOH (2 M, 0.5 mL) was added and the organic layer was separated. After anhydrification

over Na_2SO_4, the solvent was removed affording pure compound **20b** (15 mg, 80%) as an oil.

Acknowledgements

We thank MIUR (PRIN 2006) for financial support. The 'Centro Interuniversitario Lombardo per l'Elaborazione Automatica' (CILEA) is gratefully acknowledged for computational facilities.

Supplementary data

Spectroscopic discussion for compounds **17**–**20**; HPLC data for compounds **12**; X-ray data for compound (−)-**12a**; Cartesian coordinates, absolute energies, thermochemical corrections number and value of imaginary frequencies for all the stationary points herein mentioned. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.004.

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