Tetrahedron 64 (2008) 5657–5665

Contents lists available at ScienceDirect

Tetrahedron

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

β-Hydroxynorbornane amino acid derivatives: valuable synthons for the diastereoselective preparation of substituted cyclopentylglycine derivatives

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ARTICLE INFO

Article history:
Received 18 January 2008
Received in revised form 26 March 2008
Accepted 10 April 2008
Available online 12 April 2008

Keywords:
Unnatural amino acids
Retro-Dieckmann
Stereochemistry control

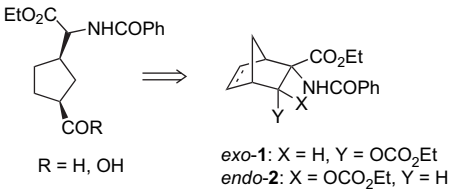
ABSTRACT

The behaviour towards the retro-aldol or retro-Dieckmann reactions of several norbornene and norbornane amino acids functionalized with an oxygen atom at C-β and characterized by different features, such as the substitution pattern and the constraints, was investigated. By C_2–C_3 disconnection new differently functionalized cyclopentenyl- and cyclopentylglycines were prepared. This synthetic approach allows to control the stereochemistry from two to four stereocentres depending on the starting norbornane derivative and affords, for each derivative, a couple of epimeric compounds at amino acid stereocentre. Depending on the features of the starting reagent and of the reaction conditions, a partial control of the stereochemistry of the amino acid carbon atom is also possible.

1. Introduction

The interest in cyclopentylglycine derivatives is well documented by recent literature[1] and is related to their biological activity, which is strictly dependent on the substitution pattern on the cyclopentyl ring.

Recently, we reported a very efficient method to prepare the above amino acid using an innovative procedure, which comprised the combination of the Diels–Alder and the retro-aldol or retro-Dieckmann reactions.[2,3] As shown in the retro-synthetic Scheme 1, both 3-formylcyclopent-3-enylglycines (R=H; see Scheme 6 for details, compounds **20**,**21**), and 3-carboxy-cyclopentylglycines (R=OH; see Scheme 7 for details, compounds **25**,**26**) were prepared using as key starting materials for their preparation the 2-amino-3-hydroxy-norbornene-2-carboxylic acid derivatives *exo*-**1** and *endo*-**2** obtained in excellent yield both in racemic and enantiopure form through a Diels–Alder reaction.



Scheme 1. Retrosynthesis of cyclopentyl and cyclopentenyl derivatives.

Here we report the preparation of new functionalized cyclopentenyl- and cyclopentylglycines, such as the epimeric 4-carboxy-cyclopentylglycines **9** and **10** (Scheme 3), functionalized with two protected hydroxy groups, the derivatives **18** and **19** (Scheme 5) in which the cyclopentylglycine scaffold is included in an heterocyclic system, and the hydroxymethyl-cyclopent-2-enylglycines **22** and **23** (Scheme 6), which are valuable synthons for further functionalizations.

These compounds are of particular biological interest because hydroxylated cyclopentylglycines can be considered carbasugar amino acids: molecules mimicking the furanose skeleton and containing the amino acid function.[4] The presence of the hydroxy groups, involved into hydrogen bonds, favours the interaction with the bioactive site. Furthermore, the insertion of a carbasugar amino acid moiety in bioactive peptides leads to peptidomimetics with improved stability towards metabolic degradation.[5]

Concerning their synthesis, it should be pointed out that the match polyfunctionalized norbornane compounds and the retro-condensation reaction are an useful way to synthesize new hetero-functionalized cyclopentylglycines with control of the stereochemistry of different centres (from two to four stereocentres), which were generated in an unambiguous, stereochemically defined manner. During these studies it was shown that the result of the retro-condensation reaction is strictly dependent both on the features of the starting norbornane derivative, mainly the presence of substituents influencing its stiffness, and on the reaction conditions, which influence the distribution of the epimers generated by disconnection of the C_2–C_3 bond in the retro-condensation reaction.

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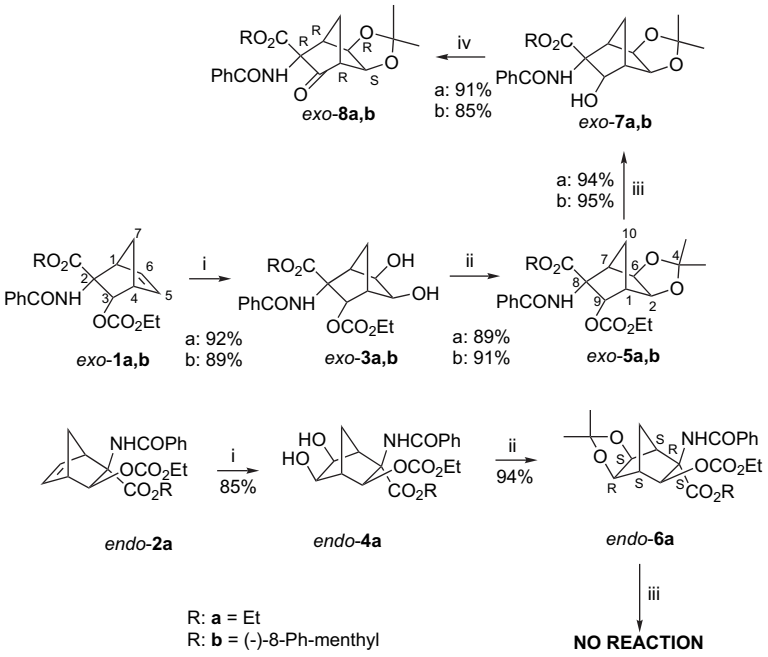
doi:10.1016/j.tet.2008.04.038



Scheme 2. Preparation of dihydroxy norbornane derivatives **8**. Reagents and conditions: (i) OsO_4, NMO, acetone/H_2O; (ii) DMP, *p*-TSA, THF; (iii) EtOH, Na_2CO_3, Δ; (iv) CH_2Cl_2, PCC.

2. Results

Norbornene derivatives *exo*-**1** and *endo*-**2** are the starting materials for the preparation of the new cyclopentylglycine derivatives **9**, **10**, **18**, **19**, **22** and **23**.

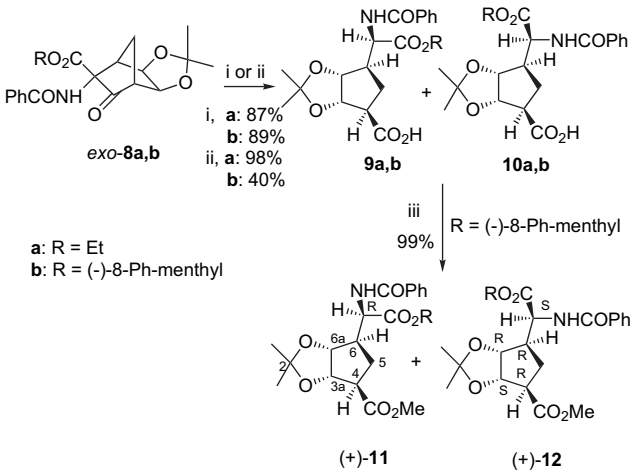
As depicted in Scheme 2, compound *exo*-**1a** was transformed into the diol derivative *exo*-**3a** (92%) by reaction with catalytic osmium tetroxide in the presence of *N*-methylmorpholine-*N*-oxide (NMO) in a mixture of acetone/H_2O.[6] The enantiopure diol (−)-*exo*-**3b** (89%) was also prepared from (−)-*exo*-**1b**[3] according to the above procedure. The hydroxy groups, cis to the carbon of the bridge, were protected using 2,2-dimethoxypropane (DMP) in the presence of catalytic *p*-toluenesulfonic acid. Acetals *exo*-**5a** and (+)-*exo*-**5b** were isolated in 89% and 91% yields, starting from *exo*-**3a** and (−)-*exo*-**3b**, respectively. Following the same synthetic protocol, it was possible to prepare *endo*-**6a** (80%, overall yield) from *endo*-**2a**, through intermediate *endo*-**4a**.

In order to remove the carbonate function, derivatives *exo*-**5a**,**b** and *endo*-**6a** were then treated with Na_2CO_3 in EtOH. None of these compounds reacted at room temperature but operating at reflux the hydroxynorbornanes *exo*-**7a** and (−)-*exo*-**7b** were formed from compounds *exo*-**5a**,**b** (**a**: 4 h, 94%; **b**: 4 h, 95%). Instead, *endo*-**6a** did not react confirming the lower reactivity of this group when it is located in the *exo* position.[2]

The hydroxy group in compounds *exo*-**7a**,**b** was oxidized using PCC in CH_2Cl_2 at room temperature and the keto derivatives *exo*-**8a** (91%) and (−)-*exo*-**8b** (85%) were formed. By applying the base-induced retro-Dieckmann reaction, the ketones *exo*-**8a** and *exo*-**8b** were transformed into the racemic epimeric glycines **9a** and **10a** and the enantiopure epimers **9b** and **10b**, respectively. Ketones *exo*-**8** were made to react both with a mixture of pyridine/water at reflux and with a mixture of acetone and DMF (9:1) using $NaHCO_3$ as the base. The distribution of compounds **9** and **10** was strictly dependent on the choice of the base. The use of pyridine gave a mixture of **9a**,**10a** (87%) and **9b**,**10b** (83%) in a 2:1 ratio (HPLC analyses), the major isomer **9** having the *R* configuration at the α-amino acid centre. Instead, the use of $NaHCO_3$ produced a 1:1 mixture of epimers (**9a**,**10a**: 98%; **9b**,**10b**: 40%).

The fact that the choice of the base can induce a different distribution of the two epimers has already been observed[2] in similar cases (see Scheme 7 and discussion).

It was possible to isolate the major stereoisomer **9a** (58%) by crystallization from the enriched mixture of epimers obtained using pyridine. Instead, enantiopure compounds **9b** and **10b** could not be separated as such. This target was achieved by transforming the acids **9b** and **10b** into the corresponding methyl esters (+)-**11** and (+)-**12** (99%) using trimethylsilyldiazomethane (Scheme 3). The above epimers were separated by column chromatography and characterized by NMR spectroscopic analyses. The absolute configurations (3a*S*,4*R*,6*R*,6a*R*) and (3a*S*,4*R*,6*R*,6a*R*) were given to epimers **11** and **12**, respectively, considering that the configuration of all stereocentres in the starting ketone was unequivocally assigned and that in the retro-condensation reaction only the C_2–C_3 bond was broken. In particular, the cis configuration of the carbon groups linked to the cyclopentyl ring in both compounds **11** and **12** was assured by the mechanism of retro-Dieckmann reaction. The



Scheme 3. Retro-Dieckmann reaction. Reagent and conditions: (i) Py, H_2O, reflux; (ii) $NaHCO_3$, acetone, DMF, reflux; (iii) $(CH_3)_3SiCHN_2$, MeOH.

configuration of the two hydroxy groups in compounds **11**,**12** is trans with respect to the other substituent. The NOESY experiment on **12** showed spatial proximity between H-5 (δ=1.63, overlapped with aliphatic protons of Ph-menthyl) and H-3a (δ=4.73) and H-6a (δ=4.32) indicating the cis relationship between these three protons. Spatial proximity between H-6a and H-6 (δ=2.17, overlapped with H-5′) was not observed proving that H-6a and H-6 are trans. Furthermore, compounds **11** and **12** showed the typical signals of NH (**11**: δ=6.75, d, J=8.7 Hz; **12**: δ=6.61, d, J=7.7 Hz) and of CH-α (**11**: δ=4.84, dd, J=8.7, 5.0 Hz; **12**: δ=4.02, dd, J=7.4, 6.7 Hz). As demonstrated for cyclopentylglycine derivatives synthesized previously in our laboratory,[2] the stereochemistry of epimeric carbon is correlated to NH and CH-α chemical shift as well as to their coupling constant (^{1}H NMR experiment). The *R* epimers are characterized by signals associated to NH and CH-α protons at lower field with respect to those of the *S* epimers. Furthermore, *R* epimers possess a bigger NH–CH_α and a smaller CH_α–CH coupling constant values with respect to those of the *S* ones. On the basis of this consideration, the (3a*S*,4*R*,6*R*,6a*R*,1′*R*) and (3a*S*,4*R*,6*R*,6a*R*,1′*S*) absolute configurations were assigned to epimers **11** and **12**, respectively.

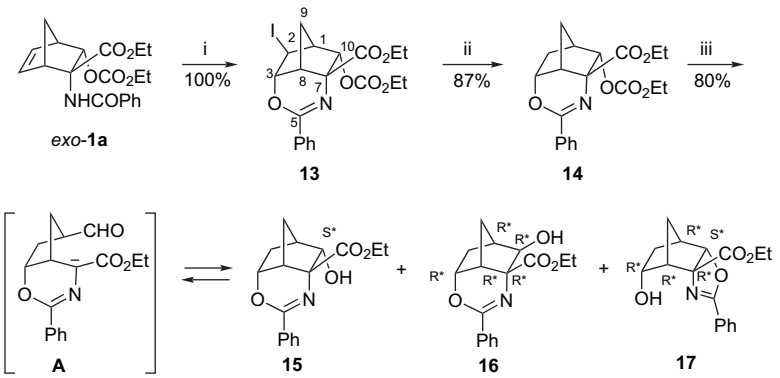
Norbornane derivative **14**, containing the oxazine ring, was prepared via iodooxazine **13** obtained in quantitative yield from compound *exo*-**1a** and *N*-iodosuccinimide (NIS) in the presence of catalytic bis-dibutylchlorotin oxide in CH_2Cl_2 at room temperature. Iodine was easily removed by treating compound **13** with (*n*-Bu)$_3$SnH in CH_2Cl_2 at reflux and compound **14** (87%) was isolated (Scheme 4).

The deprotection of the hydroxy group in oxazine **14** with Na_2CO_3 in EtOH was difficult. It did not occur at room temperature and required prolonged heating. Interestingly, the ^{1}H NMR spectroscopic analysis of the crude reaction mixture revealed the formation of different compounds. In particular, trace amounts of signals corresponding to the aldehyde proton are present, and as main compounds, a mixture of epimeric hydroxynorbornanes **15** and **16** besides the dihydrooxazole derivative **17** (1:1:3 ratio). The reaction mixture was chromatographed but only compound **16** was isolated in pure form. Every attempt to separate oxazoline **17** from oxazine **15** failed. NOESY experiment on **13** showed spatial proximity between H-10 (δ=5.52) and H-9$_x$ (δ=2.24), between H-3 (δ=5.29–5.25) and H-9$_y$ (δ=2.15) and, interestingly, between aromatic protons (δ=8.01–7.98) and the carbonate group (δ=4.2, 1.20) confirming the stereochemistry assigned to C-3 and C-10. The *exo* stereochemistry of iodine substituent was assured by the fact that H-2 (δ=4.30–4.05) has no Overhauser effect with H-9$_y$.

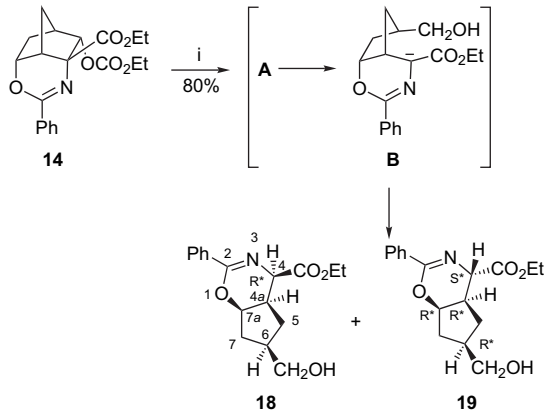
As a confirmation of the above assigned stereochemistry, NOESY experiment on parent compound **14** showed spatial proximity between H-10 (δ=5.57) and H-9$_x$ (δ=2.03), between H-3 (δ=4.88–4.79) and H-9$_y$ (δ=1.48), and between aromatic protons (δ=8.01–7.99) and the carbonate group (δ=4.35, 1.22). NOESY experiment on **15** (mixture with **17**) showed spatial proximity between H-3 (δ=5.02–4.98) and H-9$_y$ (δ=1.46), and between H-10 (δ=4.64) and H-9$_x$ (δ=1.76) indicating the *endo* stereochemistry of the hydroxy group. The change of stereochemistry of C-10 in compound **16** was confirmed by NOESY experiment. Of relevance, it was observed the spatial proximity between H-10 (δ=3.78) and *endo* H-2 (δ=1.08), between H-3 (δ=4.85–4.81) and H-9$_y$ (δ=1.6) and no spatial proximity between H-10 and H-9$_x$ (δ=2.34). ^{1}H NMR spectrum of compound **17** (mixture with **15**) showed a signal at δ=5.28 corresponding at H-2, which has an Overhauser effect with H-10$_x$ (δ=1.57). H-8 resonates at δ=4.24 which, in the NOESY experiment, showed spatial proximity with H-10$_y$ (δ=1.57), indicating the *endo* stereochemistry of the hydroxy group. The assigned structure **17**, containing the oxazoline ring, was confirmed by the chemical shift of H-2, which is at lower field with respect to the same proton on oxazine derivatives **13**–**16**. Furthermore, the ^{13}C NMR analyses revealed, as significant differences, the chemical shifts of the C-4 and of the quaternary phenyl carbon, which are at lower and at higher field, respectively (**17**: C-4, δ=167.7, quaternary phenyl carbon, δ=126.9; **13**: C-5, δ=154.3, quaternary phenyl carbon, δ=133.2; **14**: C-5, δ=154.2, quaternary phenyl carbon, δ=134.0; **15**: C-5, δ=156.5, quaternary phenyl carbon, δ=133.4; **16**: C-5, δ=153.1, quaternary phenyl carbon, δ=133.7).

These results suggest that, after deprotection of O-10, a retro-aldol condensation first occurred giving the intermediate **A** from which the two epimeric 10-hydroxy compounds **15** and **16** were formed by a new condensation reaction. This behaviour had never been observed in the case of less constrained norbornanes and suggests that the strain generated by the oxazine ring favours the retro-condensation reaction and that the protonation process of anionic intermediate **A** is slower with respect to the condensation process. Oxazoline **17** derives from **15** through an intramolecular reaction of OH-10 at C-5 affording the stable oxazoline ring. Aiming to verify these hypotheses, both pure **16** and the mixture of **15**/**17** were treated with Na_2CO_3 in EtOH at reflux for 24 h. The TLC and ^{1}H NMR spectroscopic analyses of the crude reaction mixtures revealed the presence of the three compounds, as well as of the proton associated to the aldehydes (trace amount), thus confirming that an equilibrium exists between these compounds.

Clearly, the oxazoline derivative **17**, which is the main compound, is not useful in the retro-condensation reaction. The above epimerization suggested that we prepare directly the new cyclopentenylglycine derivatives **18** and **19** using a 'one-pot' reaction consisting in the deprotection of O-10 (hydroxy compounds **15** and **16**), the retro-condensation reaction and the direct reduction of the aldehyde function. The reaction was successfully performed starting from **14** operating in EtOH at reflux in the presence of Na_2CO_3 and $NaBH_4$ (4 equiv). The new epimeric derivatives **18** and **19**, in



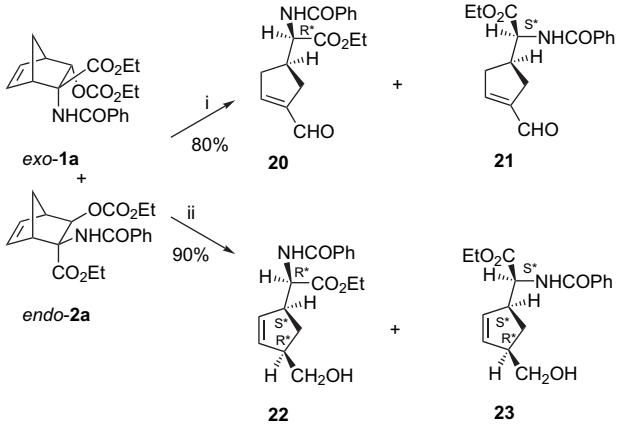
Scheme 4. Preparation of oxazine norbornane derivatives. Reagents and conditions: (i) NIS, bis-dibutylchlorotin oxide, CH_2Cl_2; (ii) (*n*-Bu)$_3$SnH, CH_2Cl_2, reflux; (iii) Na_2CO_3, EtOH, reflux.



Scheme 5. Synthesis of epimeric 6-hydroxymethyl-hexahydro-cyclopenta[*e*][1,3]-oxazine-4-carboxylic acid derivatives **18** and **19**. Reagents and conditions: (i) Na_2CO_3, $NaBH_4$, EtOH, reflux.

which the cyclopentylglycine skeleton is included in a heterocyclic system, were obtained in 80% yield (Scheme 5). The reaction is highly stereoselective and occurred with control of the stereochemistry of three stereocentres and with a partial control of the amino acid stereocentre. Isomer **19** is the more abundant (**18**/**19**, 1:4). The epimers were separated by column chromatography, and were characterized by NMR spectroscopic techniques. ^{1}H NMR spectrum of **18** showed a signal at δ=4.69 (br s) corresponding at H-7a. Spatial proximity was observed between H-7a and H-4 (δ=4.56, d, J=4.9 Hz), H-4a (δ=2.74–2.70), H-7 (δ=2.21–2.14), and H-6 (δ=2.46–2.35, weak), thus confirming the stereochemistry assigned to the molecule. Methylene protons of CH_2OH resonate at δ=3.50 and have a strong Overhauser effect with H-7 (δ=1.93) and H-5 (δ=1.37–1.32) demonstrating their cis relationship. From these data we can postulate that the stereochemistry assigned to compound **18** is (4*R**,4a*R**,6*R**,7a*R**). ^{1}H NMR spectrum of compound **19** shows a signal at δ=4.68 (br s) corresponding to H-7a. H-4 resonates at δ=4.33 (s). No spatial proximity was observed between H-7a and H-4. H-5 (δ=1.2) has a positive NOE effect with H-4 and H-7 (δ=1.9). Methylene protons of CH_2OH resonate at 3.54 and have Overhauser effect with H-5 (δ=2.20) and H-7. From these data we can postulate that the stereochemistry assigned to compound **19** is (4*S**,4a*R**,6*R**,7a*R**).

Considering this positive result, the above synthetic protocol ($NaBH_4$, 4 equiv; EtOH, 25 °C, 4 h) was applied to *exo*-**1a**. As expected, epimeric 4-hydroxymethyl-2,3-cyclopenten-2-ylglycines **22** and **23** were isolated in good yields (90%) and in a 1:1 ratio (Scheme 6). The same result was achieved starting from *endo*-**2a**,



Scheme 6. Preparation of epimeric 4-hydroxymethyl-cyclopenten-2-ylglycines. Reagents and conditions: (i) Na_2CO_3, EtOH, reflux; (ii) $NaBH_4$, EtOH, rt.

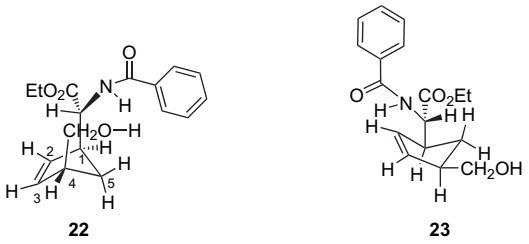
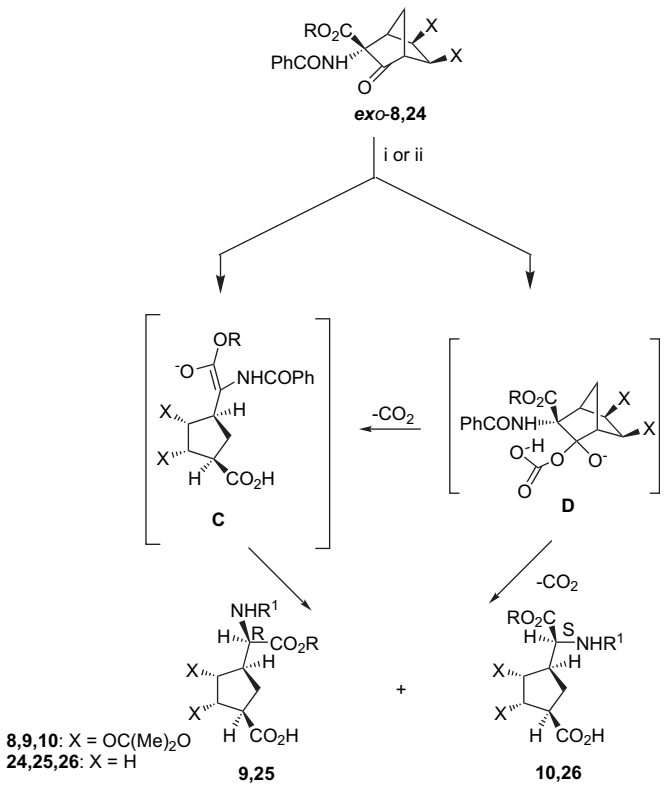


Figure 1. Conformation of compounds **22** and **23** according to NOESY experiments.

which reacted slower (7 h) with respect to the *exo* adduct, or from the mixture *exo*-**1a**, *endo*-**2a**. This synthetic method is complementary to the treatment of compound *exo*-**1a** with Na_2CO_3 in EtOH at reflux,[2] which allowed the preparation of 3,4-cyclopentenylglycines **20** and **21** (Scheme 6) in which conjugation of the double bond to the formyl group occurred.

The new compounds are characterized by a cis relationship between the two carbon residues and are epimers at the amino acid stereocentre (Fig. 1). The stereochemistry of amino acid stereocentre on **22** and **23** was tentatively assigned by NOESY experiments. Of relevance for compound (1*S**,4*R**,1′*R**)-**22**, an Overhauser effect was observed between OH (δ=2.36) and both NH (δ=7.65) and *ortho* protons of phenyl group (δ=7.84–7.80) demonstrating their spatial proximity. No NOE effect was evidenced between H-1 (δ=3.48–3.40) and H-4 (δ=2.94–2.90) thus confirming the conformation assigned to this molecule. H-α (δ=4.85) showed spatial proximity with the protons of olefin (δ=5.75–5.69) but not with H-5 at δ=1.71–1.52. The positive Overhauser effect between H-5 at δ=1.71–1.52 and NH, and proton at δ=3.64–3.61 of CH_2OH group confirm the cis relationship between this proton and the two carbon residues. As a consequence the chemical shift assigned to the parent proton H-5 is δ=2.18–2.06. The conformation of epimer (1*S**,4*R**,1′*S**)-**23** is slightly different with respect to **22**, since NOE effects were observed between H-4 (δ=3.00–2.95) and H-1 (δ=3.46–3.43, weak), H-2 (δ=5.73–5.69, weak) and H-3 (δ=5.90–5.87, strong). H-α (δ=4.80) showed spatial proximity with both H-2 (weak) and H-5 (δ=1.62–1.53, strong). Proton H-5, trans to the carbon residues, resonates at δ=2.39–2.28. Spatial proximity was found between NH (δ=6.83) and H-2, H-5 (weak). Of relevance the Ph protons do not have spatial proximity with OH (δ=1.62–1.53).

Having the results related to the synthesis of a series of cyclopentenyl- and cyclopentylglycines obtained from the transformation of several β-oxygen-substituted norbornene and norbornane amino acids characterized by different features and substitution pattern, some considerations can be made relating to the retro-condensation reactions also including results concerning the already reported retro-condensation reactions on *exo*-**1** and keto compound *exo*-**24**[3] (see Scheme 7). The reactivity of the carbonate group in the *endo* position is higher than when it is located in position *exo* (Schemes 2 and 6) thus confirming our previous results.[2,3] The retro-aldol reaction does not occur starting from 3-hydroxy-norbornane compounds (see Ref. 2 and Scheme 2) except when a further constraint is present on the ring. This is the case of oxazine derivatives (see Schemes 4 and 5) where the epimerization reaction at the oxygen-substituted carbon was observed indicating that this process is operative. The presence of sp^2 carbon atoms in the ring increases the strain too, thus favouring the retro-aldol process. In fact, depending on the reaction conditions, the direct formation of cyclopentenylglycines **20**,**21** or **22**,**23** was observed during the deprotection of 3-ethoxycarbonyloxy-derivatives *exo*-**1** and *endo*-**2** containing the double bond in the norbornane skeleton (Scheme 6). Instead, the dioxolane ring does not seem to produce sufficient strain (Scheme 2, compounds **7**). As a result, the retro-aldol condensation does not occur.



Scheme 7. Mechanism of retro-Dieckmann reaction. Reagents and conditions: (i) Py/H_2O; (ii) $NaHCO_3$, acetone/DMF.

The possibility to induce the cleavage of the C_2–C_3 bond is favoured in the presence of the keto function at C-3. The retro-Dieckmann reaction is operative in the case of compounds **8** as well as observed for the unsubstituted keto amino acid **24** (Scheme 7).

The distribution of epimeric products formed in the retro-condensation reaction depends on the features, the substitution pattern of the starting material and the reaction conditions. This aspect is intriguing since the stereochemical result observed in the formation of compounds **9**,**10** from *exo*-**8** ring differs from that observed starting from *exo*-**24** from which unsubstituted 3-carboxycyclopentylglycines **25** and **26** have been obtained. The data of the retro-Dieckmann reaction both starting from *exo*-**8** and from *exo*-**24** are summarized in Table 1 and a rationalization of the stereochemical results is proposed.

In principle, two intermediates could be involved in the retro-Dieckmann reaction: the enolate ester **C** and the monoester of carbonic acid **D**, when hydrogen carbonate was used as base (Scheme 7). Intermediate **C** was symmetrically protonated (method A), thus giving a 1:1 mixture of epimers **25** and **26** when starting from unsubstituted keto compound **24**. Instead, starting from **8** (method A), containing the oxolane ring, the protonation of enolate **C** probably occurs from the less hindered face and the (1′*R*)-**9** epimer was formed as the main compound. When method B was used, an opposite stereochemical result was observed. Starting from **24**, through the intermediate **D**, the epimer (1′*S*)-**26** was formed as the main compound by the way of an intramolecular protonation to the amino acid carbon atom when the C_2–C_3 bond was broken. In contrast, starting from ketone **8** (method B) a 1:1 mixture of epimers was formed. The increase of the isomer in which intramolecular protonation occurred (corresponding to retention of configuration, via intermediate **D**) balances the competitive protonation of the less hindered face in the intermediate **C** giving a 1:1 ratio of the two epimers.

Table 1
Stereochemical data for the retro-Dieckmann reaction

Reagent	Products	*R*/*S* ratio[a] (yield)	*R*/*S* ratio[b] (yield)
exo-**8**	**9a**,**10a**	A, 2:1 (87%)	B, 1:1 (98%)
exo-**24**	**25**,**26**	A, 1:1 (83%)[2]	B, 1:2 (75%)[2]

[a] Py/H_2O, Δ.
[b] $NaHCO_3$, acetone/DMF (9:1), Δ.

A similar stereochemical behaviour was observed starting from the phenylmenthyl derivative *exo*-**8b**. These results show that the (−)-8-phenylmenthyl chiral auxiliary does not induce asymmetric protonation of the enolate intermediate.

As reported before, the stereochemical outcome observed starting from oxazine derivative **14** gave (1′*S*)-**19** as the major isomer, the epimer in which a retention of configuration was observed. Our interpretation is that the structure of the carbanion intermediate **B** (Scheme 5), containing the hydroxymethyl group, is similar to the starting norbornane even if the C_2–C_3 bond is disconnected and that an intramolecular protonation occurs affording the *S* epimer as the main compound.

Concerning the cyclopentenylglycines **22** and **23**, as observed for the parent compounds **21**,**22**, no control in the formation of amino acid stereocentre was found and this can probably be ascribed to the formation of an unsaturated enolate intermediate like **C**.

3. Conclusion

In conclusion, we have demonstrated that the norbornene and norbornane amino acid derivatives functionalized with an oxygen atom at C-β are valuable key reagents for the preparation of functionalized cyclopentenyl- and cyclopentylglycine derivatives characterized by a various substitution pattern on the ring by the way of a retro-aldol or retro-Dieckmann reaction. In particular, the ring strain and the substitution pattern on the norbornane ring play a pivotal role in this last reaction. The new epimeric (1*R*,2*S*,3*R*,4*R*,1′*R*)- and (1*R*,2*S*,3*R*,4*R*,1′*S*)-4-(amino-carboxylmethyl)-2,3-dihydroxycyclopentanecarboxylic acid derivatives **9a**,**b** and **10a**,**b** and the new epimeric (4*R**,4a*R**,6*R**,7a*R**)- and (4*S**,4a*R**,6*R**,7a*R**)-6-hydroxymethyl-hexahydro-cyclopenta[*e*][1,3]oxazine-4-carboxylic acid derivatives **18** and **19** were prepared controlling unequivocally the stereochemistry of four and three stereocentres, respectively. A partial control of the stereochemistry of the amino acid carbon atom is also possible. Finally, the new 4-hydroxymethyl-cyclopent-2-enylglycines **22** and **23** were also efficiently prepared, which are valuable synthons for further functionalizations.

4. Experimental section

4.1. General remarks

Melting points were measured with a Büchi B-540 heating unit. ^1H NMR spectra were recorded on 200 or 500 MHz spectrometers. TLC analyses were performed on ready-to-use silica gel plates. Column chromatography was performed on silica gel [Kieselgel 60 70–230 mesh ASTM] with the solvents indicated. IR spectra were taken with a FTIR spectrophotometer. *exo*-**1a**,**b**,[2,3] *endo*-**2a**,[2] *exo*-**3a**[6] and *endo*-**4a**[6] are known compounds.

4.2. (−)-8-Phenylmenthyl (1*R*,2*R*,3*S*,4*R*,5*S*,6*R*)-2-benzoylamino-3-ethoxycarbonyloxy-5,6-dihydroxybicyclo[2.2.1]eptane-2-carboxylate (*exo*-3b)

Compound *exo*-**1b** (559 mg, 1 mmol) was suspended in a mixture of acetone/H_2O (10:1, 11 mL). After addition of *N*-methylmorpholine-*N*-oxide (400 mg, 3.42 mmol) and OsO_4 (6.84 mg, 0.02 mmol) the solution turned brown. The reaction mixture was stirred at room temperature for 2 h, then the solvent was evaporated. The crude reaction mixture was taken up with a solution of

$Na_2S_2O_4$ (20%, 12 mL) and extracted with AcOEt/THF (1:1, 24 mL). The organic layer was then washed with a solution of HCl (10%, 20 mL) and dried over Na_2SO_4. After crystallization from *i*-Pr_2O, pure compound *exo*-**3b** (546 mg, 92%) was obtained. Mp 127 °C; $[\alpha]_D^{25}$ −5 (*c* 1, $CHCl_3$); IR (Nujol) ν_{max} 3380, 1750, 1625 cm^{-1}; ^1H NMR ($CDCl_3$): δ=7.62–7.08 (m, 10H, Ar), 6.53 (s, 1H, exch., NH), 5.11 (d, *J*=4.4 Hz, 1H, H-3), 4.90–4.70 (m, 1H, CHO-Phenylmenthyl), 4.21 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 4.09 (AB system, *J*=5.9 Hz, 1H, H-5), 3.96 (AB system, *J*=5.9 Hz, 1H, H-6), 2.98 (br s, 1H, H-1), 2.90–2.60 (br s, 2H, exch., OH), 2.45 (d, *J*=4.0 Hz, 1H, H-4), 2.08–1.90 (m, 2H), 1.87 (d, *J*=12.1 Hz, 1H), 1.60–0.70 (m, 7H), 1.28 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.12 (s, 3H, Me), 1.09 (s, 3H, Me), 0.84 (d, *J*=6.2 Hz, 3H, Me) ppm; ^{13}C NMR ($CDCl_3$): δ=170.8, 168.3, 153.6, 151.2, 133.4, 132.3, 128.9, 128.4, 127.3, 125.8, 125.5, 78.1, 76.7, 68.9, 67.4, 65.1, 62.2, 50.3, 50.2, 47.5, 41.3, 40.2, 34.7, 31.6, 28.1, 27.8, 27.4, 26.0, 22.0, 14.5 ppm. Anal. Calcd for $C_{34}H_{43}NO_8$: C, 68.78; H, 7.30; N, 2.36. Found: C, 68.55; H, 7.49; N, 2.21.

4.3. General procedure for the protection of dioles

Compound *exo*-**3a**,**b** or *endo*-**4a** (1.4 mmol) was dissolved in THF (30 mL). 2,2-Dimethoxypropane (2.0 g, 16 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. The reaction mixture was stirred at room temperature for 2.5 h. (TLC: CH_2Cl_2/Et_2O; 2:1). The solvent was eliminated under vacuum, then CH_2Cl_2 (8 mL) was added and the solution was washed with water (4 mL) and dried over Na_2SO_4. After evaporation of the solvent, product *exo*-**5** (**a**: 530 mg, 85%; **b**: 790 mg, 89%) or *endo*-**6** (588 mg, 94%) was obtained.

4.3.1. Ethyl (1R,2S*,6R*,7R*,8R*,9S*)-8-benzoylamino-9-ethoxycarbonyloxy-4,4-dimethyl-3,5-dioxa-tricyclo[5.2.1.0^{2,6}]decano-8-carboxylate (exo-**5a**)*

Mp 130 °C (CH_2Cl_2/*i*-Pr_2O/*n*-pentane); IR (Nujol) ν_{max} 3370, 1725, 1645 cm^{-1}; ^{1} H NMR ($CDCl_3$): δ=7.83–7.45 (m, 5H, Ar), 6.76 (s, 1H, exch., NH), 5.18 (d, *J*=4.8 Hz, 1H, H-9), 4.48 (AB system, *J*=5.1 Hz, 1H, H-2), 4.38 (AB system, *J*=5.1 Hz, 1H, H-6), 4.35–4.16 (m, 4H, OCH_2CH_3), 3.42 (br s, 1H, H-1), 2.74 (d, *J*=4.1 Hz, 1H, H-7), 1.97 (AB system, *J*=12.1 Hz, 1H, H-10), 1.73 (AB system, *J*=12.1 Hz, 1H, H-10), 1.47 (s, 3H, Me), 1.37 (t, *J*=7.3 Hz, 3H, OCH_2CH_3), 1.28 (s, 3H, Me), 1.23 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ=171.8, 167.7, 153.7, 133.9, 132.4, 129.1, 127.5, 109.5, 77.9, 77.2, 75.7, 65.5, 62.3, 61.8, 47.3, 44.7, 28.1, 25.8, 24.5, 14.6, 14.4. Anal. Calcd for $C_{23}H_{29}NO_8$: C, 61.73; H, 6.53; N, 3.13. Found: C, 61.55; H, 6.70; N, 3.00.

*4.3.2. (−)-8-Phenylmenthyl (1R,2S,6R,7R,8R,9S)-8-benzoylamino-9-ethoxycarbonyloxy-4,4-dimethyl-3,5-dioxa-tricyclo[5.2.1.0^{2,6}]decane-8-carboxylate (exo-**5b**)*

Oil; $[\alpha]_D^{25}$ +5.5 (*c* 1, $CHCl_3$); IR (Nujol) ν_{max} 3380, 1750, 1625 cm^{-1}; ^1H NMR ($CDCl_3$): δ=780–7.02 (m, 10H, Ar), 6.27 (s, 1H, exch., NH), 5.27 (d, *J*=4.0 Hz, 1H, H-9), 4.90–4.77 (m, 1H, CHO-Phenylmenthyl), 4.44 (AB system, *J*=5.1 Hz, 1H, H-2), 4.27 (AB system, *J*=5.1 Hz, 1H, H-6), 4.24 (q, *J*=7.4 Hz, 2H, OCH_2CH_3), 3.03 (br s, 1H, H-1), 2.61 (d, *J*=4.0 Hz, 1H, H-7), 2.20–1.90 (m, 2H), 1.73 (d, *J*=11.7 Hz, 1H), 1.60–0.75 (m, 7H), 1.60 (s, 3H, Me), 1.45 (s, 3H, Me), 1.28 (t, *J*=7.4 Hz, 3H, OCH_2CH_3), 1.17 (s, 3H), 1.12 (s, 3H), 0.86 (d, *J*=6.3 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$): δ=170.8, 167.6, 153.7, 151.6, 133.9, 132.1, 128.8, 128.4, 127.5, 125.8, 125.4, 109.3, 78.1, 77.5, 76.0, 75.7, 64.9, 62.1, 50.3, 46.9, 44.7, 41.2, 40.1, 34.7, 31.6, 27.5, 27.4, 27.2, 26.4, 25.6, 24.4, 22.0, 14.5 ppm. Anal. Calcd for $C_{37}H_{47}NO_8$: C, 70.12; H, 7.47; N, 2.21. Found: C, 70.00; H, 7.60; N, 2.01.

4.3.3. Ethyl (1R,2S*,6R*,7R*,8S*,9R*)-8-Benzoylamino-9-ethoxycarbonyloxy-4,4-dimethyl-3,5-dioxa-tricyclo[5.2.1.0^{2,6}]decano-8-carboxylate (endo-**6a**)*

Mp 83 °C (cyclohexane); IR (Nujol) ν_{max} 3344, 1747, 1643 cm^{-1}; ^1H NMR ($CDCl_3$): δ=7.76–7.40 (m, 5H, Ar), 6.18 (s, 1H, exch., NH), 5.67 (d, *J*=1.9 Hz, 1H, H-9), 4.40–4.02 (m, 6H, H-2, H-6, OCH_2CH_3), 2.53 (s, 1H, H-1), 2.47 (s, 1H, H-7), 2.09 (AB system, *J*=12.4 Hz, 1H, H-10), 1.97 (AB system, *J*=12.4 Hz, 1H, H-10), 1.44 (s, 3H, Me), 1.42 (s, 3H, Me), 1.23 (t, *J*=7.3 Hz, 3H, OCH_2CH_3), 1.14 (t, *J*=7.3 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ=170.0, 168.0, 154.0, 133.7, 132.0, 128.8, 127.3, 110.6, 77.8, 77.3, 75.9, 66.1, 64.3, 62.1, 49.2, 48.1, 30.2, 27.1, 25.5, 24.3, 14.4, 14.3. Anal. Calcd for $C_{23}H_{29}NO_8$: C, 61.73; H, 6.53; N, 3.13. Found: C, 61.56; H, 6.71; N, 3.00.

4.4. Ethyl (1*S**,2*S**,3*S**,7*R**,8*R**,10*S**)-10-ethoxycarbonyloxy-2-iodo-5-phenyl-4-oxa-6-aza-tricyclo[5.2.1.0^{3,8}]dec-5-ene-7-carboxylate (13)

To a solution of *exo*-**1a** (2 g, 5.4 mmol) in CH_2Cl_2 (50 mL), NIS (1.35 g, 6 mmol) and a catalytic amount of bis-dibutylchlorotin oxide were added. The mixture turned purple and was left under stirring for 2 h (TLC cyclohexane/EtOAc, 1:1). The solution was washed with $Na_2S_2O_4$ (5%, 2×10 mL) and water (10 mL). The organic layer was anhydrified over Na_2SO_4 and concentrated under vacuum giving **13** in quantitative yield. Mp 109 °C (CH_2Cl_2/*i*-Pr_2O); IR (Nujol) ν_{max} 3051–2903, 1757, 1738, 1657 cm^{-1}; ^1H NMR ($CDCl_3$) δ=8.01–7.98 (m, 2H, Ar), 7.84–7.43 (m, 3H, Ar), 5.52 (d, *J*=4.0 Hz, 1H, H-10), 5.29–5.25 (m, 1H, H-3), 4.36–4.08 (m, 5H, H-2, OCH_2CH_3), 2.88 (d, *J*=4.0 Hz, 1H, H-8), 2.26 (d, *J*=4.8 Hz, 1H, H-1), 2.24–2.10 (m, 2H, H-9), 1.29 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.20 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ=173.0, 154.3, 153.5, 133.2, 131.4, 128.3, 127.9, 84.4, 78.7, 64.7, 62.2, 58.5, 49.7, 40.4, 31.4, 30.1, 24.6, 14.5. MS (ESI) 500.1 $(M+H)^+$. Anal. Calcd for $C_{20}H_{22}INO_6$: C, 48.11; H, 4.44; N, 2.81. Found: C, 48.00; H, 4.60; N, 2.61.

4.5. Ethyl (1*R**,3*R**,7*R**,8*R**,10*S**)-10-ethoxycarbonyloxy-5-phenyl-4-oxa-6-aza-tricyclo[5.2.1.0^{3,8}]dec-5-ene-7-carboxylate 14

To a solution of **13** (600 mg, 1.19 mmol) in anhydrous CH_2Cl_2 (6 mL), (*n*-Bu)$_3$SnH was added (346 mg, 1.19 mmol) under nitrogen atmosphere. The mixture was refluxed under stirring for 2 h and further a drop of (*n*-Bu)$_3$SnH was added (346 mg, 1.19 mmol). After 5 h the reaction was completed (TLC cyclohexane/EtOAc, 2:1). The solution was concentrated under vacuum and after column chromatography (cyclohexane/EtOAc, 100:0–1:1) **14** (387 mg, 87%) was obtained. Mp 117 °C (CH_2Cl_2/*i*-Pr_2O); IR (Nujol) ν_{max} 3068–2873, 1722, 1653 cm^{-1}; ^1H NMR ($CDCl_3$): δ=8.01–7.9 (m, 2H, Ar), 7.46–7.28 (m, 3H, Ar), 5.57 (dd, *J*=4.0, 2.2 Hz, 1H, H-10), 4.88–4.79 (m, 1H, H-3), 4.36–4.07 (m, 4H, OCH_2CH_3), 2.57 (br s, 1H, H-1), 2.25 (d, *J*=4.0 Hz, 1H, H-8), 2.15–2.03 (m, 2H, H-2, H-9), 1.73–1.48 (m, 2H, H-2, H-9), 1.32 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 1.22 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ=173.7, 154.7, 154.2, 134.0, 130.9, 128.2, 127.8, 79.4, 73.2, 64.3, 61.9, 60.1, 38.9, 38.0, 32.4, 31.5, 14.5. MS (ESI) 374.6 $(M+H)^+$. Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.17; H, 6.39; N, 3.51.

4.6. General procedure for the deprotection of the 3-hydroxy group

Compound *exo*-**5a**,**b**, *endo*-**6a** or **14** (1 mmol) was dissolved in anhydrous EtOH (20 mL). Lyophilized Na_2CO_3 (1.2 mmol) was added under stirring at reflux (TLC: CH_2Cl_2/Et_2O, 10:1). Na_2CO_3 was filtered over a Celite pad and the solvent was evaporated. Starting from compound *exo*-**5a**,**b** after crystallization of the crude reaction mixture, pure compound *exo*-**7** (**a**: 530 mg, 94%; **b**: 356 mg, 95%) was obtained. Instead starting from *exo*-**14**, a mixture of compounds **15**–**17** (20:20:60, 240 mg, 80%) was formed. It is possible to isolate compound **16** (50 mg, 17%) from **15**,**17** (150 mg, 50%) by column chromatography (from cyclohexane to cyclohexane/EtOAc, 2:1). Instead *endo*-**6a** was recovered unreacted.

4.6.1. Ethyl (1R,2S*,6R*,7R*,8R*,9S*)-8-Benzoylamino-9-hydroxy-4,4-dimethyl-3,5-dioxa-tricyclo[5.2.1.0^{2,6}]decano-8-carboxylate (exo-**7a**)*

Mp 176 °C (Et_2O); IR (Nujol) ν_{max} 3280, 1715, 1630 cm^{-1}; ^1H NMR ($CDCl_3$): δ=7.84–7.43 (m, 5H, Ar), 7.15 (s, 1H, exch., NH), 4.60 (AB system, J=6.1 Hz, 1H, H-2), 4.36 (AB system, J=6.1 Hz, 1H, H-6), 4.48–4.39 (m, 1H, H-9), 4.28–4.14 (m, 2H, OCH_2CH_3), 3.84 (d, J=4.8 Hz, 1H, exch., OH) 3.28 (br s, 1H, H-1), 2.54 (d, J=4.4 Hz, 1H, H-7), 1.87 (AB system, J=11.7 Hz, 1H, H-10), 1.56 (AB system, J=11.7 Hz, 1H, H-10), 1.47 (s, 3H, Me), 1.28 (s, 3H, Me), 1.22 (t, J=6.9 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ=172.9, 167.7, 133.6, 132.0, 128.7, 127.2, 108.9, 77.5, 75.4, 73.4, 61.9, 61.7, 46.9, 46.1, 27.6, 25.5, 24.2, 14.2. Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71; N, 3.73. Found: C, 64.03; H, 6.81; N, 3.50.

*4.6.2. (−)-8-Phenylmenthyl (1S,2S,6R,7R,8R,9S)-8-Benzoylamino-9-hydroxy-4,4-dimethyl-3,5-dioxa-tricyclo[5.2.1.0^{2,6}]decane-8-carboxylate (exo-**7b**)*

Mp 253 °C (*i*-Pr_2O); $[\alpha]_D^{25}$ +60 (c 1, $CHCl_3$); IR (Nujol) ν_{max} 3360, 1733, 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ=7.76–7.10 (m, 10H, Ar), 6.06 (s, 1H, exch., NH), 4.83–4.70 (m, 1H, CHO-Phenylmenthyl), 4.59 (AB system, J=5.5 Hz, 1H, H-2), 4.24 (AB system, J=5.5 Hz, 1H, H-6), 4.42 (br s, 1H, H-9), 2.74 (br s, 1H, H-1), 2.70 (br s, 1H, exch., OH), 2.46 (d, J=4.4 Hz, 1H, H-7), 2.20–0.80 (m, 10H), 1.46 (s, 3H, Me), 1.30 (s, 3H, Me), 1.22 (s, 3H, Me), 1.11 (s, 3H, Me), 0.88 (d, J=6.3 Hz, 3H, Me); ^{13}C NMR ($CDCl_3$): δ=172.0, 169.6, 152.2, 134.0, 132.2, 128.8, 128.3, 127.5, 125.7, 125.4, 109.1, 77.6, 77.3, 75.6, 73.0, 63.0, 50.1, 47.6, 46.1, 41.4, 39.9, 34.8, 31.5, 28.1, 27.1, 26.9, 25.7, 25.6, 24.4, 22.0. Anal. Calcd for $C_{34}H_{43}NO_6$: C, 72.70; H, 7.72; N, 2.49. Found: C, 72.59; H, 7.97; N, 2.57.

4.6.3. Ethyl (1R,3R*,7R*,8R*,10S*)-10-Hydroxy-5-phenyl-4-oxa-6-aza-tricyclo[5.2.1.0^{3,8}]dec-5-ene-7-carboxylate (**15**)*

Mixture with **17**; ^1H NMR ($CDCl_3$): δ=8.02–8.01 (m, 2H, Ar), 7.47–7.37 (m, 3H, Ar), 5.02–4.98 (m, 1H, H-3), 4.64 (br s, 1H, H-10), 4.31–4.18 (m, 2H, OCH_2CH_3), 2.61 (br s, 1H, exch., OH), 2.48 (d, J=4.4 Hz, 1H, H-8), 2.40 (br s, 1H, H-1), 2.10–1.31 (m, 7H, H-2, H-9, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ=173.9, 156.5, 133.4, 131.6, 129.0, 127.9, 87.0, 76.0, 74.3, 61.4, 40.3, 38.0, 32.3, 30.1, 14.6.

4.6.4. Ethyl (1R,3R*,7R*,8R*,10R*)-10-hydroxy-5-phenyl-4-oxa-6-aza-tricyclo[5.2.1.0^{3,8}]dec-5-ene-7-carboxylate (**16**)*

Mp 188 °C (AcOEt/hexane); IR (Nujol) ν_{max} 3415, 1728, 1652 cm^{-1}; ^1H NMR ($CDCl_3$): δ=7.96–7.92 (m, 2H, Ar), 7.46–7.34 (m, 3H, Ar), 4.85–4.81 (m, 1H, H-3), 4.30–4.24 (m, 2H, OCH_2CH_3), 3.78 (br s, 1H, H-10), 3.23 (br s, 1H, exch., OH), 2.58 (d, J=3.2 Hz, 1H, H-8), 2.36 (AB system, J=11.1 Hz, 1H, H-9), 1.60 (AB system, J=11.1 Hz, 1H, H-9), 2.34–2.23 (m, 2H, H-2, H-1), 1.61–1.05 (m, 4H, H-2, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ=172.1, 153.1, 133.7, 131.1, 128.9, 127.8, 85.2, 73.1, 69.7, 61.8, 40.3, 36.5, 36.3, 34.3, 14.7. MS (ESI) 324.3 $(M+Na)^+$. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.74; H, 6.48; N, 4.43.

4.6.5. Ethyl (1R,2S*,6R*,7R*,8R*)-8-hydroxy-4-phenyl-3-oxa-5-aza-tricyclo[5.2.1.0^{2,6}]dec-4-ene-6-carboxylate (**17**)*

Mixture with **15**; ^1H NMR ($CDCl_3$): δ=8.02–8.01 (m, 2H, Ar), 7.57–7.37 (m, 3H, Ar), 5.28 (d, J=4.5 Hz, 1H, H-2), 4.31–4.18 (m, 3H, H-8, OCH_2CH_3), 3.85 (d, J=11.3 Hz, 1H, exch., OH), 3.08 (br s, 1H, H-7), 2.74 (br s, 1H, H-1), 2.10–1.31 (m, 7H, H-2, H-9, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ=172.0, 167.8, 132.9, 129.2, 129.0, 126.9, 87.0, 83.4, 74.9, 62.3, 49.3, 42.0, 33.7, 29.0, 14.6.

4.7. General procedure for the oxidation reaction

Operating under nitrogen atmosphere, PCC (1.3 g, 6 mmol) was added to pure *exo*-**7a**,**b** (1 mmol) dissolved in CH_2Cl_2 (10 mL). The solution was stirred at room temperature for 3 h (TLC: cyclohexane/AcOEt, 1:1). The reaction mixture was filtered through a silica gel column (CH_2Cl_2/Et_2O, 10:1). Keto compound *exo*-**8** (**a**: 508 mg, 91%; **b:** 317 mg, 85%) was obtained after crystallization.

4.7.1. Ethyl (1R,2S*,6R*,7R*,8R*)-8-benzoylamino-9-oxo-4,4-dimethyl-3,4-dioxa-tricyclo[5.2.1.0^{2,6}]decano-8-carboxylate (exo-**8a**)*

Mp 175 °C (*i*-Pr_2O); IR (Nujol) ν_{max} 3400, 1765, 1725, 1674 cm^{-1}; ^1H NMR ($CDCl_3$): δ=7.83–7.40 (m, 5H, Ar), 6.56 (s, 1H, exch., NH), 4.48 (AB system, J=5.5 Hz, 1H, H-2), 4.38 (AB system, J=5.5 Hz, 1H, H-6), 4.31–4.16 (m, 2H, OCH_2CH_3), 3.69 (s, 1H, H-7), 2.96 (s, 1H, H-1), 2.43–2.33 (br s, 2H, H-10), 1.52 (s, 3H, Me), 1.30 (s, 3H, Me), 1.24 (t, J=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ=206.5, 168.2. 166.4, 133.2, 132.6, 128.9, 127.4, 111.5, 78.6, 78.0, 68.6, 63.0, 54.7, 48.3, 28.3, 25.5, 24.5, 14.2. Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.21; H, 6.40; N, 3.73.

*4.7.2. (−)-8-Phenylmenthyl (1R,2S,6R,7R,8R)-8-benzoylamino-9-oxo-4,4-dimethyl-3,5-dioxa-tricyclo[5.2.1.0^{2,6}]decane-8-carboxylate (exo-**8b**)*

Mp 260 °C (*i*-Pr_2O); $[\alpha]_D^{25}$ +30 (c 1, $CHCl_3$); IR (Nujol) ν_{max} 3400, 1765, 1725, 1674 cm^{-1}; ^1H NMR ($CDCl_3$): δ=7.74–7.06 (m, 10H, Ar), 6.34 (s, 1H, exch., NH), 5.00–4.90 (m, 1H, CHO-Phenylmenthyl), 4.46 (AB system, J=5.1 Hz, 1H, H-2), 4.39 (AB system, J=5.1 Hz, 1H, H-6), 3.47 (br s, 1H, H-7), 2.84 (br s, 1H, H-1), 2.18 (d, J=8.4 Hz, 1H), 2.15–1.89 (m, 2H), 1.70–0.80 (m, 7H), 1.49 (s, 3H, Me), 1.27 (s, 3H, Me), 1.17 (s, 6H, Me), 0.86 (d, J=6.6 Hz, 3H, Me) ppm; ^{13}C NMR ($CDCl_3$): δ=205.4, 167.6. 166.4, 151.0, 133.3, 132.4, 128.8, 128.5, 127.5, 125.7, 125.6 111.3, 78.9 78.5, 78.0, 68.5, 55.1, 50.1, 48.6, 41.9, 40.2, 34.5, 31.6, 28.0, 27.9, 27.3, 26.0, 25.5, 24.5, 21.9 ppm. Anal. Calcd for $C_{34}H_{41}NO_6$: C, 72.96; H, 7.38; N, 2.50. Found: C, 72.84; H, 7.58; N, 2.30.

4.8. General procedure for the retro-Dieckmann reaction on ketones 8a,b

Method a. Pure ketone *exo*-**8a** or *exo*-**8b** (1 mmol) was dissolved in pyridine (3 mL) and H_2O (1.5 mL). The reaction mixture was heated at reflux for 3 h (TLC: CH_2Cl_2/Et_2O, 2:1). The solvent was evaporated and the residue was taken up with a HCl solution (10%, 20 mL), which was then extracted with a mixture of THF/AcOEt (8 mL, 1:1). The organic layer was separated and dried over Na_2SO_4 giving a mixture of the two epimeric acids **9** and **10** (2:1, **a**: 500 mg, 87%; **b**: 320 mg, 83%). HPLC analyses of mixture **9**,**10a** was performed using a Licrosphere RP 18 column (12 cm×4.6 mm, H_2O/MeCN 70:30, pH=4, 0.8 mL/min; **9a**: t_R=7.9 min; **10a**: t_R=8.8 min). The crystallization of the mixture of acids **9**,**10a** from CH_2Cl_2/*i*-Pr_2O gave pure major diastereomer **9a** (330 mg, 58%). Any attempt to separate epimers **9**,**10b** failed. *Method b*. $NaHCO_3$ (46 mg, 0.55 mmol) was suspended in a mixture of acetone (4 mL) and DMF (0.4 mL). The solution was heated at reflux under nitrogen and then the ketone *exo*-**8a** or *exo*-**8b** (0.5 mmol) was added. Heating was continued for 12 h (TLC: CH_2Cl_2/Et_2O, 2:1). The solvent was evaporated and the crude reaction mixture was taken up with an aqueous solution of HCl (10%, 7 mL) and the solution was extracted with a mixture THF/EtOAc (5 mL, 1:1). The organic layer was washed with brine (2×5 mL) and dried over Na_2SO_4 giving a mixture of the two diastereomeric acids **9** and **10** (1:1, **a**: 230 mg, 98%; **b**: 385 mg, 40%).

4.8.1. (3aS,4R*,6R*,6aR*,1′R*)-6-(Benzoylamino-ethoxycarbonyl-methyl)-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylic acid **9a***

Mp 165 °C (CH_2Cl_2/*i*-Pr_2O); IR (Nujol) ν_{max} 1730, 1636 cm^{-1}; ^1H NMR ($CDCl_3$): δ=7.82–7.38 (m, 5H, Ar), 6.94 (d, J=8.4 Hz, 1H, exch.,

NH), 4.98 (dd, J=8.1, 6.1 Hz, 1H, H-α), 4.80–4.59 (m, 2H, H-3a, H-6a), 4.26 (q, J=7.0 Hz, 2H, OCH_2CH$_3$), 3.50 (br s, 1H, exch.), 3.00–2.88 (m, 1H, H-4), 2.64–2.56 (m, 1H, H-6), 2.36–2.22 (m, 1H, H-5), 1.98–1.81 (m, 1H, H-5), 1.49 (s, 6H, Me), 1.30 (t, J=7.0 Hz, 3H, OCH$_2$$CH_3$) ppm; ^{13}C NMR ($CDCl_3$): δ=177.7, 171.5, 167.7, 137.8, 132.2, 128.9, 127.4, 113.5, 82.7, 82.2, 62.2, 53.5, 49.4, 48.6, 30.9, 27.7, 25.3, 14.3. Anal. Calcd for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58. Found: C, 61.35; H, 6.59; N, 3.40.

4.8.2. (3aS,4R*,6R*,6aR*,1′S*)-6-(Benzoylamino-ethoxycarbonyl-methyl)-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylic acid* ***10a***

Mixture with **9a**; IR (Nujol) ν_{max} 1740, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.82–7.38 (m, 5H, Ar), 7.02–6.96 (d, J=7.4 Hz, 1H, exch., NH), 4.74–4.20 (m, 2H, H-3a, H-6a), 4.63 (t, J=6.9 Hz, 1H, H-α), 4.31–4.20 (m, 2H, OCH_2CH$_3$), 3.00–2.24 (m, 3H, H-4, H-5, H-6), 2.00–1.79 (m, 1H, H-5), 1.49 (s, 6H, Me), 1.24 (m, 3H, OCH$_2$$CH_3$) ppm.

*4.8.3. (3aS,4R,6R,6aR,1′R)- and (3aS,4R,6R,6aR,1′S)-6-(Benzoylamino-(−)-phenylmenthoxycarbonyl-methyl)-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylic acids (****9b****) and (****10b****)*

Mixture of epimers; IR (Nujol) ν_{max} 1740, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.82–7.08 (m, 20H, Ar), 6.65 (**9b**: d, J=8.1 Hz, 1H, exch., NH), 6.64 (**10b**: d, J=7.0 Hz, 1H, exch., NH), 4.97–4.60 (m, 6H), 4.32–4.00 (m, 2H), 3.80–3.20 (br s, 2H, exch., OH), 3.00–2.78 (m, 2H), 2.70–2.56 (m, 1H), 2.33–0.83 (m, 39H), 1.50 (s, 3H, Me), 1.47 (s, 3H, Me), 0.96 (d, J=6.3 Hz, 3H, Me), 0.88 (d, J=5.2 Hz, 3H, Me) ppm.

4.9. General procedure for the esterification reaction

To a mixture of **9**,**10b** (2:1, 100 mg, 0.2 mmol) in MeOH (6 mL), $(CH_3)_3SiCHN_2$ (2 M in Et_2O, 1 mmol, 0.5 mL) was added. After stirring under nitrogen for 30 min, the solvent was removed under vacuum and a mixture **11**,**12** (2:1, 115 mg, 99%) was obtained. Compound **11** (76 mg, 65%) was separated from **12** (38 mg, 32%) by column chromatography (SiO_2 deactivated with 1% TEA; hexane/EtOAc, 9:1).

*4.9.1. Methyl (3aS,4R,6R,6aR,1′R)-6-(benzoylamino-phenyl-menthoxycarbonyl-methyl)-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylate (****11****)*

Oil; $[\alpha]_D^{25}$ +6 (*c* 1, $CHCl_3$). IR (Nujol) ν_{max} 1760, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.85–7.08 (m, 10H, Ar), 6.75 (d, J=8.7 Hz, 1H, exch., NH), 4.98–4.91 (m, 1H, CHO-Phenylmenthyl), 4.84 (dd, J=8.7, 5.0 Hz, 1H, Hα), 4.69 (dd, J=6.4, 4.8 Hz, 1H, H-3a), 4.60 (dd, J=6.4, 4.4 Hz, 1H, H-6a), 3.72 (s, 3H, OCH_3), 2.95–2.91 (m, 1H, H-4), 2.72–2.69 (m, 1H, H-6), 2.25–2.19 (m, 1H), 2.05–1.98 (m, 2H), 1.95–1.85 (m, 1H), 1.60–0.80 (m, 6H), 1.52 (s, 3H), 1.32 (s, 6H), 1.28 (s, 3H, Me), 0.89 (d, J=6.3 Hz, 3H, Me) ppm; ^{13}C NMR ($CDCl_3$): δ=174.5, 170.0, 167.1, 150.3, 133.7, 131.8, 128.6, 128.0, 127.2, 125.5, 112.6, 83.3, 83.0, 77.3, 53.7, 52.2, 50.1, 50.0, 47.5, 41.6, 40.1, 34.3, 31.3, 29.5, 28.5, 27.5, 27.2, 25.3, 21.7 ppm. Anal. Calcd for $C_{35}H_{45}NO_7$: C, 71.04; H, 7.67; N, 2.37. Found: C, 70.80; H, 7.80; N, 2.22.

*4.9.2. Methyl (3aS,4R,6R,6aR,1′S)-6-(benzoylamino-phenylmenthoxycarbonyl-methyl)-2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylate (****12****)*

Oil; $[\alpha]_D^{25}$ +24 (*c* 1, $CHCl_3$); IR (Nujol) ν_{max} 1765, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.83–7.15 (m, 10H, Ar), 6.61 (d, J=7.7 Hz, 1H, exch., NH), 4.90–4.82 (m, 1H, H-Phenylmenthyl), 4.73 (dd, J=7.3, 5.8 Hz, 1H, H-3a), 4.32 (dd, J=7.2, 6.2 Hz, 1H, H-6a), 4.02 (dd, J=7.0, 6.7 Hz, 1H, Hα), 3.72 (s, 3H, OCH_3), 2.87–2.82 (m, 1H, H-4), 2.20–2.15 (m, 2H, H-5, H-6), 2.15–2.13 (m, 1H), 2.12–2.10 (m, 1H), 1.85–1.80 (m, 1H), 1.75–0.90 (m, 6H), 1.48 (s, 3H, Me), 1.35 (s, 3H, Me), 1.27 (s, 3H, Me), 1.24 (s, 3H, Me), 0.88 (d, J=6.8 Hz, 3H, Me) ppm; ^{13}C NMR ($CDCl_3$): δ=173.7, 170.8, 167.4, 151.8, 134.3, 132.0, 128.8, 128.3, 127.4, 125.6, 125.5, 114.0, 82.3, 81.7, 76.7, 53.7, 52.3, 50.8, 49.5, 48.7, 41.6, 39.7, 34.7, 33.1, 29.9, 29.0, 27.6, 26.7, 25.3, 22.0 ppm. Anal. Calcd for $C_{35}H_{45}NO_7$: C, 71.04; H, 7.67; N, 2.37. Found: C, 69.90; H, 7.80; N, 2.18.

4.10. Ethyl 6-hydroxymethyl-2-phenyl-4,4a,5,6,7,7a-hexahydro-cyclopentane[1,3]oxazine-4-carboxylate (18,19)

$NaBH_4$ (10 mg, 0.25 mmol) and lyophilized Na_2CO_3 (50 mg, 0.47 mmol) were added to a solution of compound **14** (100 mg, 0.25 mmol) in EtOH (10 mL). The mixture was stirred at reflux for 2 h (TLC: cyclohexane/AcOEt, 2:1). Na_2CO_3 was filtered over a Celite pad and the solvent was evaporated giving the mixture of epimers **18** and **19** (1:4, 60 mg, 80%). It is possible to separate compound **18** (10 mg, 13%) from **19** (45 mg, 63%) by flash column chromatography on silica gel (CH_2Cl_2/Et_2O, 5:1).

4.10.1. Compound (4R,4aR*,6R*,7aR*)-****18***

Mp 157 °C (AcOEt/hexane); IR (Nujol) ν_{max} 3461, 1725, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=8.01–7.94 (m, 2H, Ar), 7.44–7.30 (m, 3H, Ar), 4.69 (br s, 1H, H-7a), 4.56 (d, J=4.9 Hz, 1H, H-4), 4.31–4.22 (m, 2H, OCH_2CH$_3$), 3.50 (d, J=6.9 Hz, 2H, CH_2OH), 2.97 (br s, 1H, exch., OH), 2.74–2.70 (m, 1H, H-4a), 2.46–2.35 (m, 1H, H-6), 2.21–2.14 (m, 1H, H-7), 1.95–1.83 (m, 2H, H-5, H-7), 1.37–1.32 (m, 1H, H-5), 1.30 (t, J=6.9 Hz, 3H, OCH$_2$$CH_3$); ^{13}C NMR ($CDCl_3$): δ=172.2, 155.6, 133.8, 131.1, 129.1, 127.8, 79.4, 68.0, 61.4, 56.1, 39.8, 39.2, 36.0, 27.6, 14.7. MS (ESI) 326.4 $(M+Na)^+$. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.21; H, 7.17; N, 4.49.

4.10.2. Compound (4S,4aR*,6R*,7aR*)-****19***

Mp 177 °C (AcOEt/hexane); IR (Nujol) ν_{max} 3461, 1725, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.98–7.94 (m, 2H, Ar), 7.45–7.38 (m, 3H, Ar), 4.68 (br s, 1H, H-7a), 4.33 (s, 1H, H-4), 4.33–4.22 (m, 2H, OCH_2CH$_3$), 3.54 (d, J=6.9 Hz, 2H, CH_2OH), 2.50–2.27 (m, 2H, H-4a, H-6), 2.23–2.18 (m, 2H, H-5, H-7), 1.97–1.82 (m, 1H, H-7), 1.73 (br s, 1H, exch., OH),1.30 (t, J=6.9 Hz, 3H, OCH$_2$$CH_3$), 1.25–1.19 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ=172.9, 156.5, 139.0, 131.1, 129.0, 128.4, 127.8, 76.5, 68.0, 61.74, 57.4, 39.3, 38.9, 36.1, 31.4, 14.6. MS (ESI) 326.4 $(M+Na)^+$. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.17; H, 7.15; N, 4.52.

4.11. Ethyl benzoylamino-(4-hydroxymethyl-cyclopent-2-enyl)-acetate (22 and 23)

$NaBH_4$ (40 mg, 1 mmol) was added to a solution of compound *exo*-**1a** or *endo*-**2a** (400 mg, 1.2 mmol) in EtOH (40 mL). The mixture was stirred at room temperature (TLC: cyclohexane/AcOEt, 2:1; *exo*-**1a**: 4 h; *endo*-**2a**: 7 h). The solvent was evaporated giving the epimers **22** and **23** (1:1 ratio). It is possible to separate compound **22** (160 mg, 44%) from **23** (140 mg, 40%) by flash column chromatography on silica gel (cyclohexane/AcOEt 2:1).

4.11.1. Compound (1S,4R*,1′R*)-****22***

Mp 164 °C (AcOEt/hexane); IR (Nujol) ν_{max} 3306, 1731, 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.84–7.80 (m, 2H, Ar), 7.65 (d, J=6.8 Hz, 1H, exch., NH), 7.50–7.41 (m, 3H, Ar), 5.75–5.69 (s, 2H, H-3, H-2), 4.85 (dd, J=6.8, 4.7 Hz, 1H, H-α), 4.30–4.17 (m, 2H, OCH_2CH$_3$), 3.79–3.75 (m, 1H, CH_2OH), 3.64–3.61 (m, 1H, CH_2OH), 3.48–3.40 (m, 1H, H-1), 2.94–2.90 (m, 1H, H-4), 2.36 (br s, 1H, exch., OH), 2.18–2.06 (m, 1H, H-5), 1.71–1.52 (m, 1H, H-5), 1.32 (t, J=7.1 Hz, 3H, OCH$_2$$CH_3$); ^{13}C NMR ($CDCl_3$): δ=172.3, 168.4, 136.1, 134.5, 133.2, 131.8, 128.7, 127.7, 65.4, 61.7, 56.1, 47.9, 47.7, 26.3, 14.6. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.15; H, 7.20; N, 4.40.

4.11.2. Compound (1S,4R*,1′S*)-**23***

Mp 181 °C (AcOEt/hexane); IR (Nujol) ν_{max} 3306, 1731, 1644 cm^{-1}; ^1H NMR ($CDCl_3$): δ=7.83–7.79 (m, 2H, Ar), 7.51–7.40 (m, 3H, Ar), 6.83 (d, J=7.6 Hz, 1H, exch., NH), 5.90–5.87 (m, 1H, H-3), 5.73–5.69 (m, 1H, H-2), 4.80 (dd, J=7.6, 4.5 Hz, 1H, Hα), 4.26 (q, J=7.1 Hz, 2H, OCH_2CH_3), 3.67 (dd, J=10.4, 5.1 Hz, 1H, CH_2OH), 3.56 (dd, J=10.4, 5.1 Hz, 1H, CH_2OH), 3.46–3.43 (m, 1H, H-1), 3.00–2.95 (m, 1H, H-4), 2.39–2.28 (m, 1H, H-5), 1.62–1.53 (m, 2H, H-5, OH, 1H exch.), 1.33 (t, J=7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$): δ=172.2, 168.1, 136.1, 134.4, 132.1, 131.9, 128.9, 127.7, 66.2, 61.8, 55.9, 48.6, 47.9, 26.5, 14.6. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.25; H, 7.10; N, 4.50.

Acknowledgements

We thank Miur (PRIN 2005) for financial support.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.038.

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