Tetrahedron 67 (2011) 1907–1914

Contents lists available at ScienceDirect

Tetrahedron

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

RuO_4-catalyzed oxidation reactions of isoxazolino-2-azanorbornane derivatives: a short-cut synthesis of tricyclic lactams and peptidomimetic γ-amino acids

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ARTICLE INFO

Article history:
Received 19 October 2010
Received in revised form 9 December 2010
Accepted 6 January 2011
Available online 18 January 2011

Keywords:
Ruthenium tetraoxide
Amino acid
Lactam
1,3-Dipolar cycloadditions
Azanorbornene

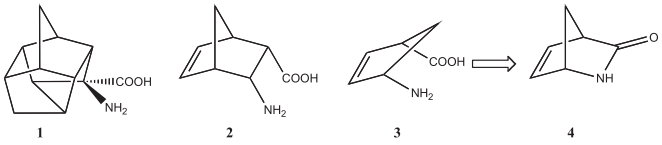
ABSTRACT

A rapid access to peptidomimetic conformationally constrained γ-amino acids has been developed through the efficient RuO_4-mediated oxidation of regioisomeric isoxazolino-2-azanorbornane derivatives. The key intermediates are tricyclic lactams, which are quantitatively hydrolyzed into the desired amino acids. The conformational analysis, conducted by means of DFT calculations, supports the use of these γ-amino acids as β-turn inducers in peptide synthesis.

1. Introduction

A great deal of attention is constantly addressed to methods for the modulation or disruption of protein–protein interactions in order to increase the knowledge of cellular processes. These current interests involve both the drug discovery industry and chemical biology and generate an intensive search for peptidomimetics.[1] Small organic molecules are privileged structures[2] of choice, and in particular unnatural amino acids,[3] to mimic the secondary structure of a specific protein. These small-sized molecules are extremely useful as traditional drug substances, while medium- and large-sized molecules (e.g., antibodies) utilize interactions involving α-helical regions of the interacting partners to disrupt protein–protein interaction.[4]

The incorporation of unnatural conformationally constrained amino acids into peptides is often used to induce precise secondary structure in adjacent regions of the peptide, the amide backbone is often maintained and then unnatural amino acids are included in the sequence.[5] Amongst the forces that induce protein folding, β-turns comprise about 25% of all residues in proteins and are determinant in the biological activity. Various types of amino acids have been proposed by different research groups as turn-inducers. Cage α-amino acids of type **1** incorporate a bulky hydrophobic disubstituted cage[6] while β-amino acids of type **2** find in the norbornene skeleton the best residue to generate a turn-inducer, also easy to prepare because of the stereoselective Diels–Alder (DA) approach.[7]



1 2 3 4

On the other hand, γ-amino acids are known as biologically active compounds in the central nervous system (CNS) of mammals and the seminal ponderous review by Ordoñez and Cativiela constitutes the obligatory reference and canon for their stereoselective synthesis.[8] Amongst the huge number of compounds reported, those including either cyclopentane or cyclopentene spacers between the amino and the carboxylic groups of type **3** are easily referred as the products of the hydrolysis of the 2-azabicyclo[2.2.1]hept-5-en-3-one **4**, a cyclic lactam obtained from the a DA cycloaddition reaction of cyclopentadiene and tosyl or mesyl cyanide.[9] Lactam **4** has found wide applications in carbocyclic nucleoside synthesis[10] because of the easy access to the required aminols. However, tosyl or mesyl cyanides used to prepare it require a potentially hazardous starting material (cyanogens chloride).[9] Although available from various chemical suppliers, the cost of both racemic and enantiopure forms is too high for large scale preparations.[11]

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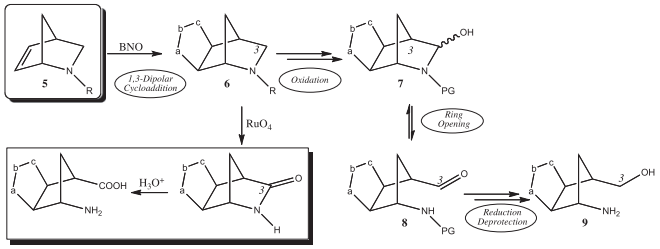
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.01.014

Recently, we have proposed a novel approach to useful aminols for the synthesis of carbocyclic nucleosides starting from a convenient source, the 2-azanorborn-5-ene **5** (Scheme 1). Structurally similar to lactam **4**, Grieco's 2-azanorborn-5-ene **5** is derived from the cycloaddition of cyclopentadiene with iminium salts generated in situ under Mannich-like conditions, in a mild and convenient aqueous aza-Diels–Alder (ADA) reaction.[12] Despite their easy availability, no attempts have been made for their use in nucleosidic syntheses or in order to prepare conveniently the lactam derivative. To this purpose the aza-methylene bridge has to be modified, precisely the carbon C3 must be oxidized by appropriate unmasking procedures.[13] The 2-azanorbornene of type **5** (Scheme 1, R=CH_2–Ph) displays a moderate dipolarophilic activity towards benzonitrile oxide (BNO) and the 1,3-dipolar cycloaddition reaction affords the regioisomeric cycloadducts of type **6**. Compared with norbornene, *N*-benzyl-2-azanorbornene still remains a highly reactive dipolarophile but less than the classical BNO trapping agent, that is, twice more reactive in apolar solvents and three times in polar or polarizable solvents.[13]



Scheme 1.

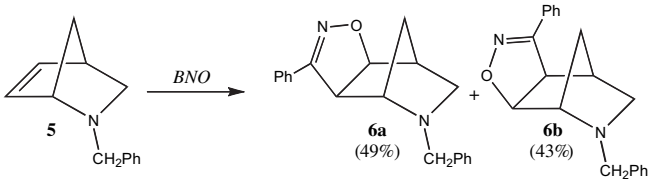
We then transformed the cycloadducts **6** into more convenient derivatives, through the oxidation to the corresponding *N*-oxides and their conversion into *N*-acetyl derivatives via the mild Polonovski rearrangement. Insertion of an acetyl as a protecting group (PG) on the 1,3-dipolar cycloadducts allowed for the oxidation at the carbon atom C3 by means of NBS/AIBN bromination reaction, which afforded a complex mixture of products whose elaboration allowed for the isolation of the protected aldehyde **8** through ring opening. Reduction of the aldehyde group and deprotection afforded the target aminols **9**. The overall protocol required from the beginning eight steps to prepare the aminols **9**, which were further converted into the desired adenine nucleosides.[14]

In the search for a fast and convenient oxidation protocol we took advantage of the oxidative ability of RuO_4, a strong oxidizing agent. Since its introduction into organic chemistry more than fifty years ago,[15] RuO_4-catalyzed reactions in a biphasic system were often considered to be sluggish or unselective.[16] Two recent papers by Petride and co-workers[17] dealing with the RuO_4-mediated oxidation of *N*-benzylated tertiary amines (cyclic and acyclic) prompted us to test the RuO_4 on our tricyclic isoxazolino-2-azanorbornane derivatives of type **6** probing the regioselectivity of the oxidation process with the aim to get straightly the carbonyl functionality in the position C3 of the azanorbornane moiety to prepare the lactams **10** and from these latters the γ-amino acids **11** under hydrolytic conditions.

2. Results

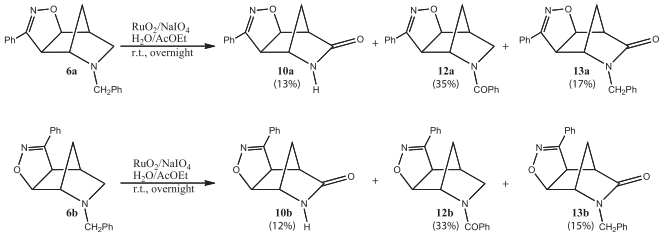
2.1. The oxidation of the regioisomeric *N*-benzyl isoxazolino-2-azanorbornane cycloadducts

N-Benzyl-2-azanorborn-5-ene **5** was prepared by addition of freshly distilled cyclopentadiene to an aqueous solution of benzylamine hydrochloride and 37% aqueous formaldehyde in an ADA reaction according to the well-known procedure.[12a] The 1,3-dipolar cycloaddition of BNO with **5** was performed by generating the 1,3-dipole with the in situ procedure,[18] affording the two regioisomeric cycloadducts **6a** and **6b** in 49% and 43% yields, respectively (Scheme 2).[13]



Scheme 2.

The regioisomeric cycloadducts **6a** and **6b** were oxidized by using the catalytic system RuO_2/$NaIO_4$ with the H_2O/AcOEt biphasic conditions (Scheme 3).[19] The protocol needs only a catalytic amount of the expensive $RuO_2 \cdot H_2O$ (20 mol %) in the presence of 2.5 equiv (with respect to the substrate to be oxidized) of sodium periodate as oxidant in order to regenerate the oxidizing species RuO_4 at the highest oxidation state after the end of the catalytic cycle.[20] Typically, $RuO_2 \cdot H_2O$ is added to a solution of $NaIO_4$ in water in inert atmosphere and left under stirring for 30 min. The formation of the RuO_4 species at the highest oxidation state becomes clear because of the bright yellow colour solution.



Scheme 3.

At this point, the substrates dissolved in ethyl acetate are added in one portion. The reaction mixture instantly turns an opaque-black colour. The cycloadducts **6a**,**b** disappear almost completely in the reaction time (TLC) and the formation of three new products is observed. *N*-benzoyl derivatives **12a**,**b** are the major products (35% and 33%, respectively) obtained upon the oxidation of the more reactive benzylic methylene group. Oxidation of the C3 of the azanorbornene moiety afforded the *N*-benzyl-lactams **13a**,**b** in 17% and 15% yields, respectively. Finally, lactams **10a**,**b** were also found and isolated in 13% and 12% yields, respectively. The isolation of the oxidized products displayed some difficulties, which is reflected in the yields of the pure compounds. The mixtures were in fact diluted with ethyl acetate before a first filtration through a Celite pad. The organic layer was washed with a saturated $NaHSO_3$ solution ensuring precipitation of Ru-black. This required a second filtration through a Celite pad and a final washing with brine of the organic phase. Presumably, this long and tedious work-up procedure does not permit the complete recovery of the polar oxidized products, which could in principle also act as ligands in ruthenium complexes. A simplified work-up was then applied to the oxidation reactions by diluting the reaction mixture with ethyl acetate and washing immediately with a saturated $NaHSO_3$ solution. Ru-black and other impurities were filtered off through a Celite pad and the organic phase dried and submitted to chromatographic separation to isolate the products.

This resulted in an increase of the reaction yields of about 10% with respect to the yields of the products reported in Scheme 3. The structures of all the products rely upon their analytical and spectroscopic data. Lactams **10a**,**b** derive from the RuO_4-mediated oxidation on the C3 of the azanorbornane moiety and de-benzylation reaction. The presence of the carbonyl groups is testified in the IR spectra by the stretching bands in the expected regions and in the ^{13}C NMR spectra by the signals at δ 177.2 and 178.5, respectively, for the two regioisomers. The IR spectra also showed the NH bands around 3250 cm^{-1}. The ^1H NMR spectra clearly showed the presence of the NH groups giving broad singlets at δ 6.76 and 5.88, for **10a** and **10b**, respectively, while the presence of the isoxazoline protons H4 and H5 as doublets (J=8 Hz) between δ 4.2 and 5.3 indicated that the oxidation had no effects on the heterocyclic rings. The structural assignments were confirmed through X-ray analyses of single crystals. Fig. 1 reports the ORTEP views of lactam **10a** and **10b**.

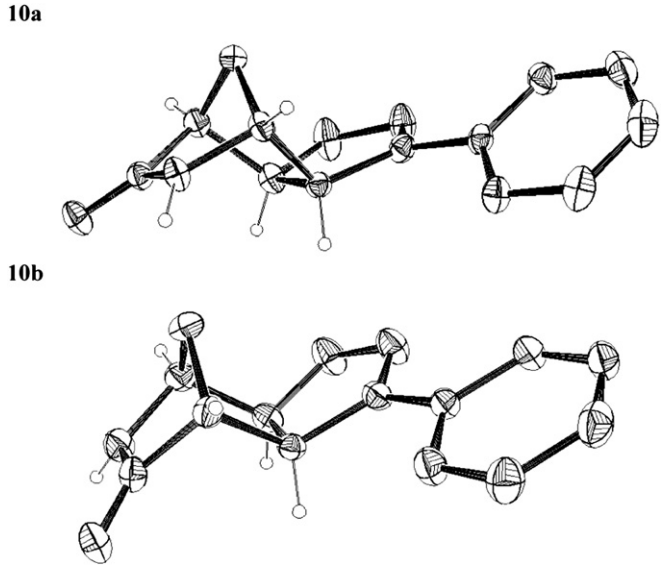
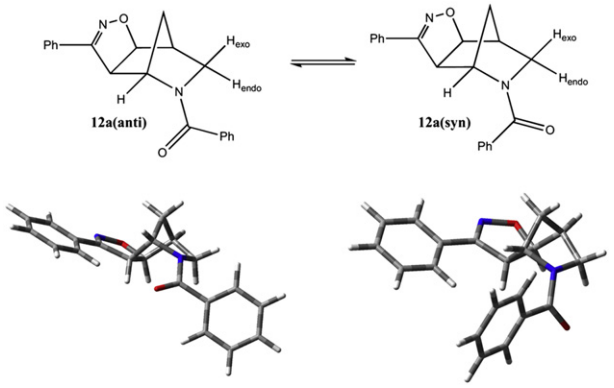


Fig. 1. ORTEP plots of lactams **10a** and **10b** with atom labelling (ellipsoid at 20% probability). Hydrogen atoms are omitted for clarity, except for the isoxazoline ring protons, bridgehead protons and NH.

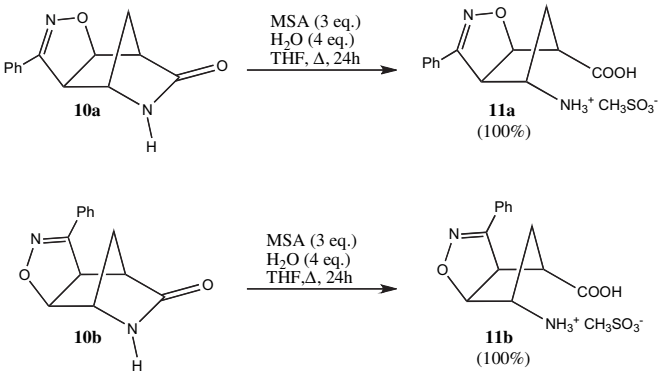
N-benzoylated compounds **12a**,**b** derive from the starting cycloadducts through the oxidation of the highly reactive methylene of the exocyclic benzylic moiety. This is not an unexpected result since Petride and co-workers had already demonstrated the facile oxidation of the benzyl group in the RuO_4-mediated oxidation of *N*-benzylated tertiary amines.[17] The absence of the benzylic methylene is clearly shown in the ^1H NMR spectra and the presence of the benzoyl carbonyl group is indicated by stretching IR bands in the expected regions and by the signals in the ^{13}C NMR spectra at between δ 168.0 and 170.0. The structures are confirmed by the presence of the signals referred to the methylene in C3 between δ 3.1 and 3.7 and the H4 and H5 protons of the isoxazoline ring in the typical range.

While the NMR spectra of the regioisomer **12b** exhibits resolved signals in all the regions, the regioisomer **12a**, where the two phenyl groups are on the same side with respect to the norbornane moiety, showed only a couple of distinguishable signals both in ^1H and ^{13}C spectra. For a better understanding of the nature of these features, the NMR spectra were recorded in DMSO at room temperature and 80 °C, allowing for the detection of the presence at room temperature of two rotamers in slow equilibrium. Upon heating, the two sets of signals in the proton spectra coalesce. The two rotamers are indicated as **12a**(*anti*) and **12a**(*syn*), where *anti* and *syn* refer to the relative position of the phenyl groups. We have identified the major rotamer as **12a**(*anti*), in the ratio 1.7:1 with the minor **12a**(*syn*), on the base of sizeable anisotropic effects of the amide group,[21] which cause deshielding of the hydrogen atoms proximal to the carbonylic oxygen atom and shielding of the hydrogen atoms proximal to the aromatic ring. Thus, the two rotamers exhibit similar energies but the presence of the aromatic rings on the same side or the tricyclic structure shifts the equilibrium towards the rotamer **12a**(*anti*). The assignments were established with the aid of ^{13}C NMR and corroborated by the appropriate $^{13}C-^1H$ COSY (HSQC) experiment, which show the C1–N signal at δ 60.5 in the major rotamer **12a**(*anti*) while in the minor rotamer **12a**(*syn*) the same signal is shielded and found at δ 57.5. A similar behaviour is observed in the case of the AB system for the methylene in the C3; the signals are splitted apart one each other when the carbonyl group is directed towards the methylene in the minor rotamer **12a**(*syn*). A NOESY experiment showed a selective cross-peak correlating the *ortho*-aromatic protons of the benzoylic ring with hydrogen atom *exo* of the C3 methylene group belonging to the major rotamer **12a**(*anti*).



When the oxidation of the azanorbornene moiety occurs on the C3 carbon atom *N*-benzyl-lactams **13a**,**b** are obtained. The exocyclic benzylic methylene group survives oxidation and gives, in the ^1H NMR spectra, the typical AB system array between δ 4.2 and 4.6. The newly formed carbonyl groups give in the ^{13}C NMR spectra signals at δ 173.5 and 175.2 for **13a** and **13b**, respectively, while the IR spectra show the stretching bands of the C=O groups in the expected regions.

The transformation of the lactams **10a**,**b** into the desired γ-amino acids **11a**,**b** was secured by the easy and quantitative hydrolysis in the presence of 3 equiv of methanesulfonic acid (MSA) and 4 equiv of water in THF at reflux for 24 h.[22] Insoluble methanesulfonic acid salts of the regioisomeric amino acids **11a**,**b** separate from the organic solution and the products are easily isolated in quantitative yields by simple filtration (Scheme 4).



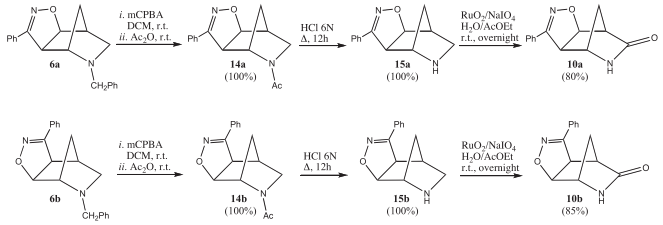
Scheme 4.

The structures of the γ-amino acids **11a**,**b** rely upon their analytical and spectroscopic data. In the IR spectra two intense and broad bands in the region 3210–2500 cm^{-1} are found indicative of the presence of the carboxylic groups, while the carbonyl groups gave two bands at 1729 and 1716 cm^{-1}, respectively. In the ^1H NMR spectra the carboxylic acid protons are found at δ 13.10 and 13.06 as singlets for **11a** and **11b**, respectively, while the NH_3^+ protons are found at δ 8.11and 8.23. The presence of the heterocyclic rings fused to the cyclopentane moieties are clearly indicated by the isoxazoline protons at δ 5.46 (H5, d, *J*=9 Hz) and 4.44 (H4, d, *J*=9 Hz) for compound **11a** and at δ 5.20 (H5, dd, *J*=11, 5 Hz) and 4.67 (H4, dd, *J*=11, 6 Hz) for compound **11b**.

The *N*-benzoyl cycloadducts **12a**,**b** cannot be further oxidized at the carbon C3 through the RuO_2 protocol presumably because of the complexation of ruthenium at the carbonyl group. Control experiments performed with cycloadducts **12a**,**b** in the presence of different amounts of $RuO_2/NaIO_4$ allowed for the recover of unaltered starting materials. Every attempt to submit the *N*-benzyl lactams **13a**,**b** to hydrogenolysis failed because of the amide group, which does not allow for the detachment of the benzyl group from the amidic nitrogen.

2.2. More efficient and expedite route to lactams

The direct oxidation of the 1,3-dipolar cycloadducts of BNO to *N*-benzyl 2-azanorbornene **6a**,**b** afforded a pool of oxidized compounds, only 20% of which is useful for the preparation of the target amino acids. The remaining 80% is represented by the products derived from the oxidation of either the C3 or the benzylic methylene. This prolific composition of the reaction mixtures is undoubtably due to the presence of the benzyl group in the starting cycloadducts. In order to remove of the benzyl substituent, we took advantage of the already applied protocol of replacement through the oxidation of the regioisomeric cycloadducts **6a**,**b** to the corresponding *N*-oxides, followed by the Polonovski rearrangement to prepare the *N*-acetyl derivatives **14a**,**b** in quantitative yields.[13] A facile hydrolysis with boiling HCl 6 N for 12 h afforded quantitatively the deprotected cycloadducts **15a**,**b** (Scheme 5) whose structures were easily attributed through their spectroscopic data.



Scheme 5.

In the IR spectra the NH bands are found at 3318 and 3320 cm^{-1} and the NH proton is clearly visible in the ^1H NMR spectra at δ 1.91 and 1.59 for **15a** and **15b**, respectively. In the aromatic region of the proton spectra, a single phenyl group belonging to the isoxazoline ring is shown. By applying the oxidation protocol with $RuO_2/NaIO_4$, the cycloadducts **15a**,**b** were converted in good yields into the desired lactams **10a**,**b**. The same protocol can be successfully applied to the *N*-benzoyl derivatives **12a**,**b**, which can be quantitatively transformed into the amines **15a**,**b** allowing for the recover of the major components of the oxidation reaction mixtures directly obtained from the oxidation of the cycloadducts **6a**,**b**. Subsequent hydrolysis of the lactam prepared through the new route afforded the amino acids **10a**,**b** in high yields (>80%).

2.3. Peptidomimetic ability

The facile hydrolysis of these lactams **10** afforded the desired amino acids **11** whose structure are well designed to induce β-turn in peptides. To analyze the type of turns exhibited by a peptidomimetic derivative, a brief summary of the β-turn conventions and definitions is required.[1] The definition of β-turn refers to a tetrapeptide in a turned conformation where the amino group of the fourth amino acid forms a hydrogen-bond with the C=O group of the first amino acid as represented in the Fig. 2. A critical distance is defined between the Cα carbon atoms, which must be <7 Å. A second requirement is the distance between the carbonyl oxygen of the first amino acid and the amide hydrogen of the fourth one, which must be <4 Å. In general the use of cage amino acids allows for the induction of a β-turn by the complete replacement of the three amino acids required normally.

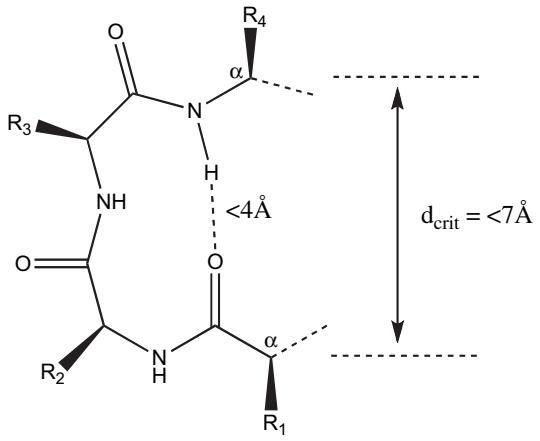


Fig. 2. Criteria for the identification of β-turns.

The conformational analysis of the 2,3-oxaza[3.3.0]bicyclooct-3-ene derivatives discloses their potential use as peptidomimetic compounds. When fused to an isoxazoline ring or similar rings[23] the cyclopentane moiety usually adopts an envelope conformation with the flap directed towards the isoxazoline ring thus giving a boat-like appearance to the structure. When the flap is directed away from the isoxazoline ring, the resulting chair-like conformation is usually higher in energy. Fig. 3 shows the B3LYP/6-31G*[24] optimized structure of the boat-like and chair-like conformations of the parent 2,3-oxaza[3.3.0]bicyclooct-3-ene as a model where the phenyl group has been replaced with a methyl for sake of simplicity in calculations.

The boat-like conformation allows for the relief of non-bonded interactions between the heterocyclic ring and the substituents on the adjacent cyclopentane carbons and cause the dihedral angles between the isoxazoline protons and the adjacent *trans* cyclopentane protons to be near 90°. The chair-like conformation is higher in energy by 1.6 kcal/mol and the dihedral angles range about 140°. When introducing formyl and amino substituents in the *trans* cyclopentane positions to mimic the C=O···H–N interactions, the differences between the boat and chair conformations remain essentially the same as in the parent systems, i.e., supporting a preferential faced location of the two groups. When the formyl and amino groups are replaced by amide groups as in peptide models (E) and (F) the gap between boat and chair conformation increases favouring the boat ones while the hydrogen-bonding distances are maintained in the required range.

The boat conformations are then preferred to be involved in a peptide skeleton. The distances involved in the intramolecular

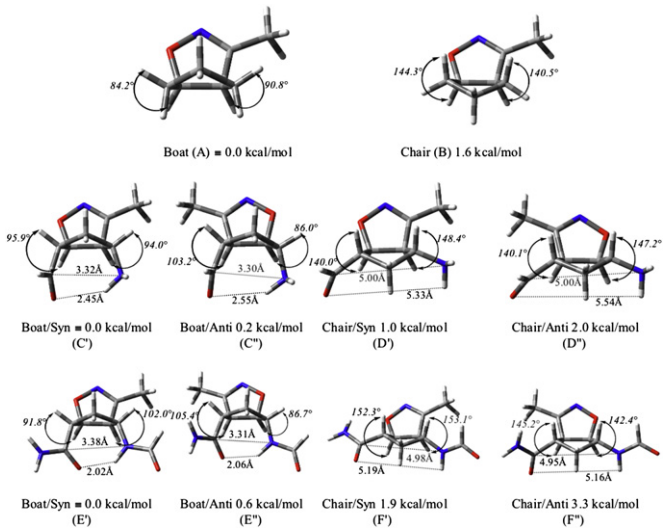


Fig. 3. Boat- and chair-like conformations of 2,3-oxaza[3.3.0]bicyclooct-3-ene (A) and (B). Relative energies are given near the conformational labels. Curved arrows specify the dihedral angles in degrees between the bridgehead protons and the protons of the adjacent methylenes. Dotted lines indicate hydrogen-bonds along with C═O···N distances in Å. *syn* (′) and *anti* (″) labels refer to the relative positions of the substituent on the nitrile oxide moiety and the NH_2 group. Models of boat- and chair-like conformations of 2,3-oxaza[3.3.0]bicyclooct-3-ene derivatives (C) and (D) with a formyl and an amino substituents in the *trans* cyclopentane positions are also reported along with peptide models (E) and (F).

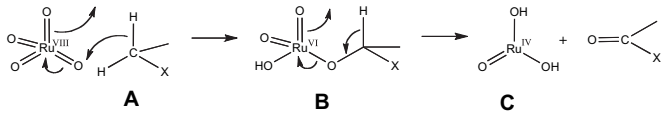
hydrogen-bonding are given in the figure and correspond well to cases of strong hydrogen-bonding in the case of boat conformers.[25]

If we consider the more stable boat conformations the distance between the amino nitrogen atom and the carbonyl group ranges around 3.3 Å while the hydrogen-bond between the amino hydrogen and the carbonyl oxygen is about 2.5 Å, i.e., less than the 4 Å required to induce a β-turn.

3. Discussion and conclusion

The RuO_4-catalyzed oxidation protocol has been applied to the isoxazolino-2-azanorbornane derivatives in the search of an expedite and selective oxidation towards lactam derivatives as precursors of peptidomimetic γ-amino acids. The results obtained with the RuO_4-mediated oxidation of tricyclic heterocyclic systems constitute a new probe of the oxidation mechanism and regioselectivity.

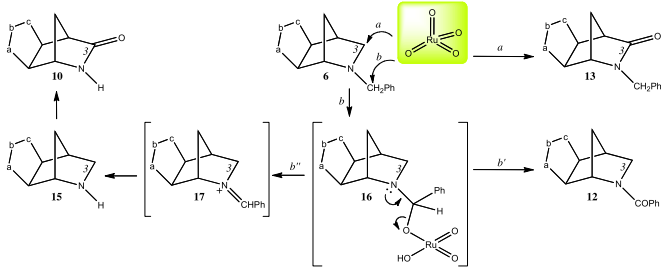
Ruthenium tetroxide was firstly employed by Djerassi in 1953 in diol synthesis and conversion of sulfides into sulfones or sulfoxides.[15] Due to its high reactivity, it was mainly used in diol synthesis from alkenes or oxidative fragmentation of aromatic compounds. RuO_4 was considered for a long time too reactive and unselective. The reactions required a biphasic system of organic solvent and water to be performed, determining a few problems in isolation of the polar oxidized products. Four decades later, Piccialli and Shing reported an efficient and selective dihydroxylation of olefins, the first successful application of this metal oxide.[26] RuO_4 is a tetrahedral 16-electron d^0 species, isoelectronic to OsO_4 but a much more powerful oxidizing agent.[16] Oxidation of C–H bonds represent the most intriguing property of the ruthenium tetroxide as oxidant in 1,2-dehydrogenation of alcohols and amines as well as in 1,1-dehydrogenation of saturated hydrocarbons, a quite uncommon process but extremely useful from the synthetic point of view, allowing for the introduction of oxidated functionalities on activated methylenes.[19] The mechanism proposed by Bakke[27] and widely recognised in its validity is shown in Scheme 6. The oxidation process takes place in two separate steps: (1) oxidative addition of RuO_4 to the C–H bond (A) through a concerted transition



Scheme 6.

state (TS) yielding the metal alcoholate with a reduced Ru(VI) (B); (2) fragmentation of the metal alcoholate affording the carbonyl compound while Ru(VI) is reduced at Ru(IV) (C), which must be re-oxidized to Ru(VIII) by the sodium periodate to re-start the catalytic cycle.[16,19,28]

The regioselectivity of the oxidation of heterocyclic compounds and in particular of *N*-benzylated tertiary amines (morpholine, piperidine, pyrrolidine) has already been discussed by Petride and coworkers;[17] they showed that in these systems where two different methylenes (exocyclic and endocyclic) are activated by the same nitrogen atom, the oxidation reaction proceeds with poor regioselection and both the methylene are involved affording two different amides.[29] These findings correspond well to our results with the tricyclic compounds at hand. Cycloadducts **6** undergo oxidation by RuO_4 on both the endocyclic (path a) and exocyclic (path b) methylenes affording the amides **12** and **13** in the ratio 2:1 with a preference for the benzylic methylene (Scheme 7). In the case of path b, the Ru(VI) complex of type **16** can undergo to oxidation of the benzylic methylene to afford the benzoyl derivative **12** (path b′) or alternatively undergo the elimination (path bi″) of stable benzaldehyde through the iminium ion of type **17** affording the 2-azanorbornane derivative **15**, which undergoes a further oxidation occurring exclusively on the endocyclic C3 carbon atom to give the final lactam **10**.



Scheme 7.

The strong directing effect produced by the presence of a benzylic group in the oxidation can be only avoided by eliminating the group itself.

The transformation from the 1,3-dipolar cycloadducts **6** to the *N*-acetyl derivatives **14** is the method to prepare the 2-azanorbonane derivative **15** and allows for an efficient high yielding route to the lactam **10**. In principle, the simple 2-azanorborn-5-ene are available from the ADA cycloaddition between cyclopentadiene, ammonium chloride and formaldehyde, but the low reaction yields and the high instability of the product towards cycloreversion[12] limit somewhat this approach.[30]

In conclusion, we have developed a short synthetic procedure for the synthesis of peptidomimetic γ-amino acids conformationally constrained because of the fused heterocyclic ring to the cyclopentane moiety and able to act as turn-inducers. The key intermediates are the lactams **10a**,**b** whose preparation can be either performed starting from the regioisomeric cycloadducts to the *N*-benzyl 2-azanorbornene **6a**,**b** or the corresponding derivatives **14a**,**b** taking advantage of the efficient oxidation by RuO_4 whose selectivity on active methylenes has been discussed. The preferences

of the 2,3-oxaza[3.3.0]bicyclooct-3-ene derivatives for a boat conformation support the possible use of the amino acids **11a**,**b** as β-turn inducers in peptide synthesis. Inclusion of this type of unnatural amino acids in a peptide sequence will also benefit of the additional features, which characterize the synthesized compounds, where the presence of an isoxazoline ring allows for the establishment of hydrogen-bonds from polar residues of peptide side chains as well as the phenyl substituent is able to be inserted in a hydrophobic pocket generated by other amino acid residues. Samples of compounds **10a**,**b** will be soon submitted to a short peptide synthesis to confirm these expectations.

4. Experimental section

4.1. General

All melting points are uncorrected. Elemental analyses were done on a C. Erba 1106 elemental analyzer available in our Department. IR spectra (Nujol mulls) were recorded on an FT-IR Perkin–Elmer RX-1. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 in the specified deuterated solvents. Chemical shifts are expressed in ppm (δ) from internal tetramethylsilane. Column chromatography and TLC: silica gel 60 (0.063–0.200 mm) (Merck); eluant cyclohexane/ethyl acetate from 9:1 to 5:5. MPLC: Biotage FMP apparatus equipped with KP-SIL columns, eluant cyclohexane/ethyl acetate from 9:1 to 7:3. The identification of samples from different experiments was secured by mixed mps and superimposable IR spectra.

4.2. Materials

Benzhydroximoyl chloride, prepared according to the reported method,[31] has been used to prepare BNO by treating with distilled Et_3N in a typical in situ cycloaddition reaction in the presence of *N*-benzyl 2-azanorborn-5-ene **5**. Cycloadducts **6a**,**b** have been isolated according to the previously published procedure.[13] Ruthenium(IV) oxide hydrate ($RuO_2 \cdot H_2O$) and sodium periodate are from Sigma–Aldrich and were used without purification.

4.3. Oxidation reactions of cycloadducts 6a,b

$RuO_2 \cdot H_2O$ (0.51 g, 3.9 mmol) was added to a solution of 10.6 g (49 mmol) $NaIO_4$ in 15 mL of water under inert atmosphere (N_2) and left stirring for 30 min. The formation of the RuO_4 species at the highest oxidation is indicated when the colour solution turns into a bright yellow colour. At this point, 6 g (20 mmol) of cycloadducts **6a**,**b** are dissolved in the minimum amount of ethyl acetate (75 mL) and added to the ruthenium solution in two portions. The reaction mixtures turn immediately an opaque-black colour and a further 4 g (19 mmol) of sodium periodate are added to ensure the presence of active RuO_4. Monitoring of the reactions by TLC allows for the identification of the disappearance of the starting material; typically the reactions are completed after one night. The mixtures are diluted with ethyl acetate (150 mL) and treated with $NaHSO_3$ saturated solution (100 mL) for a couple of hours until metal ruthenium separates off. Filtration through a Celite pad provides a clear organic phase, which is washed with water and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude mixtures are submitted to chromatographic separation to isolate the products.

Compound **10a**: (0.59 g, 13%), white powder, mp 166–169 °C from ^{i}Pr$_2$O. IR: ν_{max} 3306, 1712 cm^{-1}. R_f (cyclohexane/ethyl acetate 1:1) 0.23. ^{1}H NMR: δ ($CDCl_3$) 1.96 and 2.10 (d, 1H+1H, *J* 10.5 Hz, CH_2); 3.21 (s, 1H, CH–CO); 4.22 (d, 1H, *J* 8 Hz, H4$_{isox.}$); 4.25 (s, 1H, CH–N); 5.28 (d, 1H, *J* 8 Hz, H5$_{isox.}$); 6.76 (b, 1H, NH); 7.45 (m, 3H, arom.); 7.75 (m, 2H, arom.). ^{13}C NMR: δ ($CDCl_3$) 35.5, 52.6, 57.7, 60.6, 84.4, 126.2, 127.6, 128.8, 130.1, 154.6, 177.2. Anal. Calcd for $C_{13}H_{12}N_2O_2$ (MW=228.25): C, 68.41; H, 5.30; N, 12.27. Found: C, 68.38; H, 5.29; N, 12.30.

Compund **10b**: (0.55 g, 12%), white powder, mp 176–179 °C from ^{i}Pr$_2$O. IR: ν_{max} 3203, 1710 cm^{-1}. R_f (cyclohexane/ethyl acetate 1:1) 0.20. ^{1}H NMR: δ ($CDCl_3$) 1.81 (dd, 1H, *J* 11, 1 Hz, H–CH); 1.85 (dd, 1H, *J* 11, 1 Hz, HC–H); 2.95 (s, 1H, CH–CO); 4.16 (s, 1H, CH–N); 4.20 (d, 1H, *J* 8 Hz, H4$_{isox.}$); 5.11 (d, 1H, *J* 8 Hz, H5$_{isox.}$); 5.88 (b, 1H, NH); 7.44 (m, 3H, arom.); 7.75 (m, 2H, arom.). ^{13}C NMR: δ ($CDCl_3$) 35.2, 47.2, 53.7, 59.3, 87.5, 126.8, 128.9, 129.9, 130.5, 155.3, 178.5. Anal. Calcd for $C_{13}H_{12}N_2O_2$ (MW=228.25): C, 68.41; H, 5.30; N, 12.27. Found: C, 68.39; H, 5.31; N, 12.29.

Compound **12a**: (2.23 g, 35%), colourless crystals, mp 205–208 °C from Benzene/Ligroin. IR: ν_{max} 1633 cm^{-1}. R_f (cyclohexane/ethyl acetate 1:1) 0.37. Major rotamer **12a**(*anti*): ^{1}H NMR: δ (DMSO) 1.43 and 1.65 (d, 1H+1H, *J* 11 Hz, CH_2); 2.95 (s, 1H, *CH*–CH_2); 3.14 (d, 1H, *J* 11 Hz, H_{endo}–CH); 3.42 (dd, 1H, *J* 11, 4 Hz, HC–H_{exo}); 4.03 (s, 1H, CH–N); 4.25 (d, 1H, *J* 8 Hz, H4$_{isox.}$); 4.99 (d, 1H, *J* 8 Hz, H5$_{isox.}$); 7.59 (m, 8H, arom.); 7.80 (m, 2H, arom.). ^{13}C NMR: δ (DMSO) 31.8, 43.1, 45.7, 58.1, 60.5, 85.4, 126.3, 126.7, 128.0, 128.6, 128.8, 129.9, 130.2, 136.9, 154.8, 168.6. Minor rotamer **12a**(*syn*): ^{1}H NMR: δ (DMSO) 1.55 and 1.75 (d, 1H+1H, *J* 11 Hz, CH_2); 2.87 (s, 1H, *CH*–CH_2); 2.99 (d, 1H, *J* 10 Hz, H_{endo}–CH); 3.63 (dd, 1H, *J* 10, 4 Hz, HC–H_{exo}); 4.16 (d, 1H, *J* 8 Hz, H4$_{isox.}$); 4.67 (s, 1H, CH–N); 4.90 (d, 1H, *J* 8 Hz, H5$_{isox.}$); 7.59 (m, 8H, arom.); 7.80 (m, 2H, arom.). ^{13}C NMR: δ (DMSO) 30.1, 44.2, 49.5, 56.6, 57.5, 85.0, 126.4, 127.6, 128.3, 128.5, 129.1, 130.3, 130.6, 135.6, 155.1, 169.2. Anal. Calcd for $C_{20}H_{18}N_2O_2$ (MW=318.37): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.42; H, 5.69; N, 8.75.

Compound **12b**: (2.10 g, 33%), colourless crystals, mp 156–157 °C from Benzene/Ligroin. IR: ν_{max} 1711 cm^{-1}. R_f (cyclohexane/ethyl acetate 1:1) 0.30. ^{1}H NMR: δ ($CDCl_3$) 1.77 (m, 2H, CH_2); 2.86 (s, 1H, *CH*–CH_2); 3.40 (d, 1H, *J* 11 Hz, H–CH); 3.67 (dd, 1H, *J* 11, 3 Hz, HC–H); 3.90 (d, 1H, *J* 8 Hz, H4$_{isox.}$); 4.40 (s, 1H, CH–N); 4.99 (d, 1H, *J* 8 Hz, H5$_{isox.}$); 7.48 (m, 6H, arom.); 7.55 (m, 2H, arom.); 7.77 (m, 2H, arom.). ^{13}C NMR: δ ($CDCl_3$) 30.8, 39.4, 50.3, 56.1, 62.7, 85.5, 126.8, 126.9, 128.1, 128.6, 130.1, 133.3, 135.7, 156.6, 169.8. Anal. Calcd for $C_{20}H_{18}N_2O_2$ (MW=318.37): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.47; H, 5.71; N, 8.76.

Compound **13a**: (1.10 g, 17%), white plates, mp 142–144 °C from AcOEt. IR: ν_{max} 1703 cm^{-1}. R_f (cyclohexane/ethyl acetate 1:1) 0.40. ^{1}H NMR: δ ($CDCl_3$) 1.82 (d, 1H, *J* 10 Hz, H–CH); 1.97 (dd, 1H, *J* 10, 1 Hz, HC–H); 3.33 (s, 1H, CH–CO); 3.75 (d, 1H, *J* 8 Hz, H4$_{isox.}$); 3.95 (s, 1H, CH–N); 4.38 and 4.55 (AB syst., 2H, *J* 15 Hz, CH_2–Ph); 5.15 (d, 1H, *J* 8 Hz, H5$_{isox.}$); 7.42 (m, 10H, arom.). ^{13}C NMR: δ ($CDCl_3$) 26.8, 34.6, 45.7, 54.0, 58.4, 61.4, 85.1, 126.4, 127.9, 128.3, 128.7, 129.1, 130.3, 135.7, 154.9, 173.5. Anal. Calcd for $C_{20}H_{18}N_2O_2$ (MW=318.37): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.43; H, 5.68; N, 8.77.

Compound **13b**: (0.95 g, 15%), white plates, mp 162–165 °C from AcOEt. IR: ν_{max} 1702 cm^{-1}. R_f (cyclohexane/ethyl acetate 1:1) 0.36. ^{1}H NMR: δ ($CDCl_3$) 1.74 (d, 1H, *J* 11 Hz, H–CH); 1.97 (d, 1H, *J* 10 Hz, HC–H); 3.10 (s, 1H, CH–CO); 3.98 (s, 1H, CH–N); 4.16 (d, 1H, *J* 8 Hz, H4$_{isox.}$); 4.26 and 4.56 (AB syst., 2H, *J* 15 Hz, CH_2–Ph); 4.84 (d, 1H, *J* 8 Hz, H5$_{isox.}$); 7.46 (m, 8H, arom.); 7.77 (m, 2H, arom.). ^{13}C NMR: δ ($CDCl_3$) 34.3, 45.5, 48.3, 54.4, 63.0, 85.8, 126.8, 128.0, 128.1, 128.4, 128.9, 129.0, 133.5, 155.5, 175.2. Anal. Calcd for $C_{20}H_{18}N_2O_2$ (MW=318.37): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.46; H, 5.69; N, 8.79.

4.4. Hydrolysis of lactams 10a,b

In a round-bottom flask, 0.17 g (0.79 mmol) of lactams **10a**,**b** were dissolved in 25 mL of THF and 0.15 mL (2.36 mmol) of MSA are added along with 0.06 mL (3.16 mmol) of water. The mixture was heated at reflux for 2 days. The white solids of the amino acid **11a**,**b** quantitatively separate from the solution and are collected by filtration in pure form as methanesulfonic salt.

Compound **11a**: (0.27 g, 100%), white crystals, mp>200 °C (dec) from THF. IR: ν_{max} 3050, 1729 cm^{-1}. R_f (ethyl acetate) 0.10. ^{1}H NMR:

δ (DMSO) 2.15 (m, 2H, CH_2); 2.30 (s, 3H, $CH_3SO_3^-$); 3.15 (m, 1H, *CH*–COOH); 3.77 (b, 1H, CH–N); 4.44 (d, 1H, *J* 9 Hz, $H4_{isox.}$); 5.46 (dd, 1H, *J* 9, 3 Hz, $H5_{isox.}$); 7.49 (m, 3H, arom.); 7.78 (m, 2H, arom.); 8.11 (s, 3H, NH_3^+); 13.06 (b, 1H, COOH). ^{13}C NMR: δ (DMSO) 32.3, 40.7, 52.1, 54.7, 57.7, 89.2, 127.5, 128.2, 129.4, 130.7, 156.2, 174.6. Anal. Calcd for $C_{14}H_{18}N_2O_6S$ (MW=342.37): C, 49.11; H, 5.30; N, 8.18. Found: C, 49.09; H, 5.29; N, 8.20.

Compound **11b**: (0.27 g, 100%), white crystals, mp>210 °C (dec) from THF. IR: ν_{max} 2950, 1719 cm^{-1}. R_f (ethyl acetate) 0.10. ^{1}H NMR: δ (DMSO) 1.98 (m, 1H, H–CH); 2.28 (m, 1H, HC–H); 2.31 (s, 3H, $CH_3SO_3^-$); 3.01 (q, 1H, *J* 8 Hz, *CH*–COOH); 3.70 (m, 1H, CH–N); 4.67 (dd, 1H, *J* 11, 6 Hz, $H4_{isox.}$); 5.20 (dd, 1H, *J* 11, 5 Hz, $H5_{isox.}$); 7.48 (m, 3H, arom.); 7.70 (m, 2H, arom.); 8.23 (s, 3H, NH_3^+); 13.10 (b, 1H, COOH). ^{13}C NMR: δ (DMSO) 33.2, 40.1, 46.5, 54.4, 57.5, 88.2, 126.9, 127.9, 129.0, 130.4, 158.1, 174.4. Anal. Calcd for $C_{14}H_{18}N_2O_6S$ (MW=342.37): C, 49.11; H, 5.30; N, 8.18. Found: C, 49.12; H, 5.28; N, 8.20.

4.5. Hydrolysis of *N*-acetyl derivatives 14a,b and *N*-benzoyl derivatives 12a,b

In a round-bottom flask, 2.68 g (10 mmol) of *N*-acetyl derivatives **14a**,**b** or *N*-benzoyl derivatives **12a**,**b** were suspended in HCl 6 N and the mixtures were heated at reflux for 24 h until disappearance of the starting material. The resulting solutions are neutralized with $NaHCO_3$ and the products extracted with dichloromethane (DCM, 2 × 100 mL). The organic phases are dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure to leave the crude 2-azanorbornane derivatives in quantitative yields.

Compound **15a**: (2.14 g, 100%), white powder, mp 116–119 °C from ^{i}Pr$_2$O. IR: ν_{max} 3318, 1559 cm^{-1}. R_f (Chloroform/Methanol 9:1) 0.20. ^{1}H NMR: δ ($CDCl_3$) 1.46 and 1.74 (d, 1H+1H, *J* 11 Hz, CH_2); 1.91 (s, 1H, NH); 2.57 (d, 1H, *J* 10 Hz, CH_2–N); 2.84 (s, 1H, *CH*–CH_2); 2.92 (d, 1H, *J* 10 Hz, CH_2–N); 3.73 (s, 1H, CH–N); 3.74 (d, 1H, *J* 8 Hz, $H4_{isox.}$); 4.82 (d, 1H, *J* 8 Hz, $H5_{isox.}$); 7.41 (m, 3H, arom.); 7.74 (m, 2H, arom.). ^{13}C NMR: δ ($CDCl_3$) 32.2, 43.3, 44.3, 57.5, 59.7, 86.2, 126.7, 128.7, 128.9, 129.9, 155.8. Anal. Calcd for $C_{13}H_{14}N_2O$ (MW=214.26): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.89; H, 6.59; N, 13.10.

Compound **15b**: (2.14 g, 100%), white powder, mp 109–112 °C from ^{i}Pr$_2$O. IR: ν_{max} 3320, 1560 cm^{-1}. R_f (Chloroform/Methanol 9:1) 0.20. ^{1}H NMR: δ ($CDCl_3$) 1.51 and 1.66 (d, 1H+1H, *J* 11 Hz, CH_2); 1.59 (s, 1H, NH); 2.71 (s, 1H, *CH*–CH_2); 2.72 (d, 1H, *J* 9 Hz, CH_2–N); 2.96 (dd, 1H, *J* 9, 3 Hz, CH_2–N); 3.70 (s, 1H, CH–N); 3.71 (d, 1H, *J* 8 Hz, $H4_{isox.}$); 4.71 (d, 1H, *J* 8 Hz, $H5_{isox.}$); 7.43 (m, 3H, arom.); 7.74 (m, 2H, arom.). ^{13}C NMR: δ ($CDCl_3$) 31.8, 39.3, 48.7, 55.9, 59.4, 87.1, 126.7, 128.2, 128.7, 129.9, 156.6. Anal. Calcd for $C_{13}H_{14}N_2O$ (MW=214.26): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.86; H, 6.61; N, 13.08.

4.6. Oxidation reactions of cycloadducts 15a,b

$RuO_2 \cdot H_2O$ (0.24 g, 2 mmol) is added to a solution of 4.7 g (22 mmol) $NaIO_4$ in 15 mL of water under an inert atmosphere (N_2) and left under stirring for 30 min. The formation of the RuO_4 species at the highest oxidation is indicated when the colour solution turns into a bright yellow colour. At this point, 1.9 g (9 mmol) of cycloadducts **6a**,**b** are dissolved in the minimum amount of ethyl acetate (25 mL) and added to the ruthenium solution in two portions. The reaction mixtures turn immediately an opaque-black colour and further 1 g (4.8 mmol) of sodium periodate are added to ensure the presence of active RuO_4. Monitoring of the reactions by TLC allows for the identification of the disappearance of the starting material; typically the reactions are completed after one night. The mixtures are diluted with ethyl acetate (50 mL) and treated with $NaHSO_3$ saturated solution (50 mL) for a couple of hours until metal ruthenium separates off. Filtration through a Celite pad provides a clear organic phase, which is washed with water and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude products **10a**,**b** are submitted to chromatographic purification. Spectroscopic analyses confirmed that the compounds are identical to authentic specimens previously prepared.

Acknowledgements

Financial support by the University of Pavia (Fondo d'Ateneo per la Ricerca, FAR), MIUR (PRIN 2008) and EUTICALS S.p.a.—V.le Milano, 86/88—26900 Lodi, Italy is gratefully acknowledged. The authors wish to thank the Fondazione Banca del Monte di Lombardia for a research grant. Thanks are due to Dr. Massimo Boiocchi (CGS) for X-ray data collection. The authors wish to thank warmly Prof. P. Caramella for fruitful suggestions and helpful discussion.

Supplementary data

Crystal structure analyses of lactams **10a** and **10b**, CCDCs 796635 (*a*=9.813), 796636 (*a*=9.303), respectively. Cartesian Coordinates of calculated boat- and chair-like conformations. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.01.014.

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