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Reactivity of β-amino alcohols against dialkyl oxalate: synthesis and mechanism study in the formation of substituted oxalamide *and/or* morpholine-2,3-dione derivatives

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ABSTRACT

The reactivity of various β-amino alcohols with dialkyl oxalates, in several reaction conditions, has been investigated. Linear disubstituted oxalamides were obtained with primary β-amino alcohols and linear tetrasubstituted oxalamides, or a mixture of linear tetrasubstituted oxalamides and cyclic morpholine-2,3-diones were obtained with *N*-substituted β-amino alcohols. A DFT study of the possible mechanism has been made. The theoretical results indicate that these reactions are not kinetically controlled, there is an equilibrium between all species and therefore follow a thermodynamic control. The different behavior between the primary β-amino alcohols and *N*-methyl β-amino alcohols is due to the greater stability of linear disubstituted oxalamides with respect to linear tetrasubstituted oxalamides. The energy of tetrasubstituted oxalamides is closer to the energy of the corresponding morpholine-2,3-diones.

1. Introduction

Amino alcohol functional groups are often found in many bioactive compounds and their stereoselective synthesis and reactions are of wide interest.[1] Among the numerous 1,2-amino alcohols, the aryl amino alcohols, such as ephedrine **1f**, pseudoephedrine **1g**, norephedrine **1h**, are of particular interest (Fig. 1).[2] 1,2-Amino alcohols have an outstanding significance as precursors of oxalamides **2** and morpholine-2,3-diones **3**. Oxalamides and morpholine-2,3-diones are important substructures in compounds that show biological activity including HIV-1 protease inhibitors,[3] cephalosporin bactericides,[4] and chemioterapic agents.[5]

The new retro-bispeptides having the oxalamide moiety located at the center has become of great interest. The retro-bispeptides have been used in protein engineering to generate non coded α-amino acids[6] as well as to prepare bioactive peptides with enhanced stability toward enzymatic degradation.[7] Moreover, oxalamide linkages are also of great importance in the material science field, since they are included in the aliphatic polyamides.[8] On the

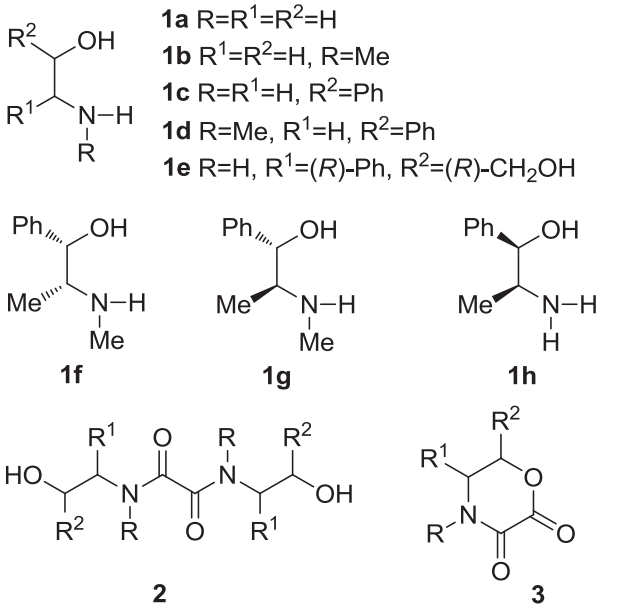

Fig. 1. Amino alcohols **1**, oxalamides **2**, and morpholine-2,3-diones **3**.

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other hand, the bis(amino acid)- and bis(amino alcohol)-oxalamide gelators represent the class of versatile compounds whose gelation ability is a consequence of strong and directional intermolecular hydrogen bonding provided by oxalamide units.[9]

The synthesis of oxalamide function occurs in a variety of ways, among them, the reaction of primary amines and dialkyl oxalate to obtain dialkyl oxalamides.[10] Since secondary amines react only slowly and incompletely with diethyl oxalate, the tetraalkyl oxalamides were prepared from amines and oxalyl chloride in the presence of a tertiary amine.[11] Frequently, in order to afford *N*-substituted oxalamides, the synthetic approach involves several steps, as N-alkylation once oxalamide was formed.[12]

The use of β-amino alcohols in the reaction with dialkyl oxalate, to obtain oxalamides, it seems very interesting. In this case the presence of the hydroxyl group can also lead to the production of cyclic morpholine-2,3-diones.[13] It is therefore possible to obtain both linear oxalamides and cyclic morpholine-2,3-diones. Nevertheless, there are no reports in the literature of a detailed study on the reactivity of β-amino alcohols toward dialkyl oxalate in different reaction conditions.

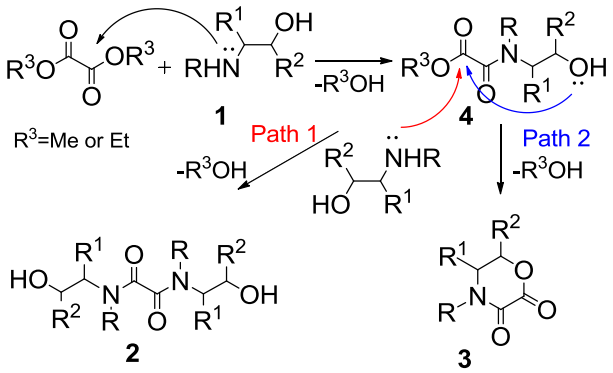
Continuing our research in the chemistry of amino alcohols,[14] the aim of this paper is the study of the potential influence of the substituents of the β-amino alcohols, as well as the reaction conditions, on the conversion into oxalamides and morpholine-2,3-diones. To this end, we have carried out a study of the reaction of some β-amino alcohols with diethyl oxalate. Moreover, a possible mechanism of reaction is suggested, which is based on DFT calculations and additional experimental evidences. The theoretical study has been carried out in vacuum and in several solvents in order to study the energy changes in different media.

2. Results and discussion

This work will be focused on three steps: firstly, the description of the experimental results from the reaction of β-amino alcohols **1a**–**1h** with diethyl oxalate. Secondly, the study of the possible reaction mechanisms by theoretical calculations and, finally, additional experiments were carried out in order to support the proposed mechanism.

2.1. Experimental studies

The β-amino alcohols **1a**–**1h** were subjected to reaction with diethyl oxalate to afford the linear oxalamides **2a**–**2h** and the morpholine-2,3-diones **3b**, **3d**, **3e**, and **3g** (see Scheme 1). The reactions were initially performed with 2 equiv of amino alcohol and 1 equiv of oxalate, which are the stoichiometric amounts to obtain the linear oxalamides **2**.



a R=R^1=R^2=H
b R^1=R^2=H, R=Me
c R=R^1=H, R^2=Ph
d R=Me, R^1=H, R^2=Ph
e R=H, R^1=(*R*)-Ph, R^2=(*R*)-CH$_2$OH
f R=Me, R^1=(*R*)-Me, R^2=(*S*)-Ph
g R=Me, R^1=(*S*)-Me, R^2=(*S*)-Ph
h R=H, R^1=(*S*)-Me, R^2=(*R*)-Ph

Scheme 1. Simplified mechanism.

In order to study the influence of the solvent, toluene and ethanol are used. The reactions have also been carried out at room temperature and refluxing of solvents, showing similar results at both temperatures. The products of these reactions, at room temperature, are shown in Table 1.

Table 1
Reaction of 2 equiv of β-amino alcohols **1a**–**1h** with 1 equiv of diethyl oxalate in toluene or in ethanol

Amino alcohol	Toluene		Ethanol	
	Products	Yield (%)	Products	Yield (%)
1a	**2a**	94[a]	**2a**	76[a]+19[b]
1c	**2c**	96[a]	**2c**	77[a]+18[b]
1e	**2e**	96[a]	**2e**	76[a]+19[b]
1h	**2h**	88[a]+3[b]	**2h**	13[a]+7[b]
	4h	6[b]	**4h**	65[b]
1b	**2b**	96[b]	**2b**	90[b]
			3b	4[b]
1d	**2d**	84[a]+5[b]	**2d**	92[b]
1f	**2f**	90[a]+3[b]	**2f**	95[b]
	3f	3[b]	**3f**	Traces
1g	**2g**	76[a]+12[b]	**2g**	83[b]
	3g	4[b]	**3g**	12[b]

[a] Precipitated product.
[b] Product obtained from the mother liquor (the filtrate liquid), or the crude reaction mixture. Yield calculated from ^{1}H NMR.

As it can be seen in Table 1, the reaction of primary β-amino alcohols **1a**, **1c**, and **1e** with diethyl oxalate afforded the corresponding linear disubstituted oxalamides (**2a**,[15] **2c**, and **2e**[14b] in Scheme 1), in toluene and also in ethanol. In all cases the yield is almost quantitative. When toluene is used the product precipitates, while in ethanol part of product remains in the mother liquor and we have to proceed with its concentration. In the reaction of norephedrine **1h** with diethyl oxalate in toluene, 88% of the corresponding oxalamide **2h** precipitates. An analysis of the mother liquor reveals the presence of an additional 3% of oxalamide **2h**[16] with 6% of a product that is identified as the oxamidic ester intermediate **4h**.[17] When the reaction is performed in ethanol, only 13% of the oxalamide **2h** precipitates. The presence of the intermediate **4h** in the mother liquor increases to 65% of the reaction.

These intermediate products **4** had already been observed in the reaction of primary amino alcohols with dialkyl oxalate to obtain cyclic morpholine-2,3-diones **3**.[17] Failure to achieve cyclization to the cyclic morpholine-diones **3** was attributed to conformational energy barriers inhibiting rotation around the secondary amide bond and formation of the *cisoid* dicarbonyl conformation, necessary for obtaining the final cyclic compound **3**.[17b] However, as we explain later, there is not a problem of energy barriers (kinetic control) but energy balance (thermodynamic control), and the presence of this intermediate is probably due to its stability under the reaction conditions. When the solvent used is ethanol, the stability increases considerably. In all reactions, the presence of cyclic morpholine-2,3-diones was not detected.

Slightly different results were obtained in the reaction of *N*-substituted β-amino alcohols (**1b**, **1d**, **1f**, and **1g**) with diethyl oxalate. In the reaction of **1d**, **1f**, and **1g** in toluene, the corresponding linear oxalamide precipitates (between 76 and 90% yield). An analysis of the mother liquor revealed the presence of an additional amount of oxalamide (between 3 and 12% yield) and in some cases (**1f**, **1g**) a small proportion of cyclic morpholine-2,3-dione (about 4%). However, into the reaction of amino alcohol **1b** with diethyl oxalate in toluene there is no precipitation. In the crude of reaction the mayor product is the oxalamide **2b**[14a] (96% yield). When reactions

were carried out in ethanol, due to the absence of precipitate, the concentrate is analyzed. The major product is the corresponding linear tetrasubstituted oxalamide **2**, but in some cases there was an increase in the proportion of cyclic morpholine-2,3-dione (12% in the case of **3g**).

These results indicate that in the reaction of β-amino alcohols with diethyl oxalate the reaction pathway 1 is favored (see Scheme 1), leading almost exclusively to the oxalamide **2**. The result is independent of the solvent used, toluene or ethanol. However, the appearance of the morpholine-2,3-dione **3** in the reaction with *N*-substituted β-amino alcohols, points to a competition between the reaction pathway 1 and pathway 2 in Scheme 1. With the use of ethanol instead of toluene, the formation of cyclic compound is slightly favored.

The spectroscopic data of compounds **2a**,[15] **2b**,[14a] **2e**,[14b] **2h**,[16] **3b**,[18] **3d**,[18] **3f**,[19] and **4h**[17] were in complete agreement with those reported in the literature. To our knowledge, products **2c**, **2d**, **2f**,[20] **2g**, and **3g** are new, and their structures were confirmed by spectroscopic data (see Experimental data). As calculated in previous work,[14a] in solution linear oxalamides **2b**, **2d**, **2f**, and **2g**, can be found as mixture of three conformers (**cc**, **ct**/**tc**, and **tt**) due to the high rotational barrier of the amide bond. The three conformers, present different signals and the ^{1}H and ^{13}C NMR spectra will be very complex.

In order to explain the different observed reactivity of the β-amino alcohols and *N*-substituted β-amino alcohols with diethyl oxalate, we have made a complete theoretical study of the possible mechanisms of reaction.

2.2. Theoretical study

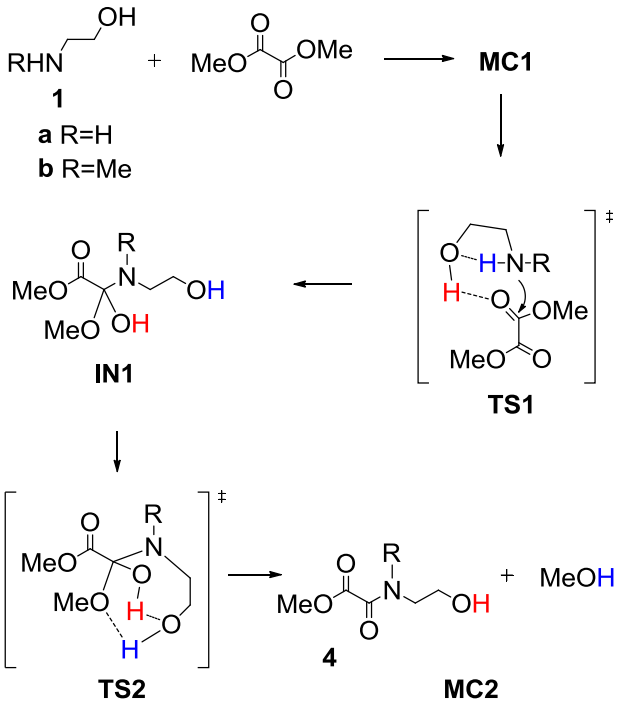
The purpose of this section is the study of a possible reaction mechanism and the evaluation of the kinetic or thermodynamic control of these reactions.

In the Scheme 1, we can see the simplified mechanistic pathways (Path 1 and Path 2) which, starting from the β-amino alcohols and reacting with the dialkyl oxalate can lead to the final linear oxalamides **2** or the cyclic morpholine-2,3-diones **3** .The two paths share a common intermediate **4**. The formation of this intermediate is produced by intermolecular nucleophilic substitution of an alkoxide of the dialkyl oxalate by the amino group of the amino alcohol. In the first pathway (Path 1), intermediate **4** is converted into oxalamide **2** through another intermolecular nucleophilic substitution of the alkoxide remainder in **4** with a second molecule of amino alcohol. Cyclic morpholine-2,3-diones **3** arises from the intramolecular attack of the hydroxyl group of the intermediate **4** to the carbonyl group of the ester moiety with extrusion of alkoxide group (Path 2).

For the theoretical study we have selected the compounds **1a** and **1b** and the dimethyl oxalate. Firstly, we will discuss the formation of the intermediate **4**, and later we will study the conversion of **4** into the oxalamide **2** and morpholine-2,3-dione **3**.

*2.2.1. Kinetic study: formation of the intermediate **4**.* The complete suggested mechanism for the conversion of amino alcohols **1a** and **1b** into the intermediate **4**, in a two-steps process, is presented in Scheme 2. We have also studied the same conversion in a single-step process (see Scheme 1S, Figs. 1S–4S and Table 1S in Supplementary data). This single-step process has a higher energy and only the two-steps mechanism is discussed. The free energies of the species are in Table 2 and Fig. 2. The geometries of species involved in the mechanism are in the Supplementary data (see Figs. 3S–4S).

Initially, the reactants form a molecular complex (**MC1**), which is converted into intermediate **4**, through transition state **TS1** and **TS2**. **TS1** arises from the intermolecular attack of the amino group



Scheme 2. Mechanism for the conversion of amino alcohols **1a** and **1b** into the intermediate **4**.

Table 2
B3LYP/6-31G** relative free energies (ΔG, in kcal/mol), in vacuo, of the stationary points involved in the reaction of dimethyl oxalate with **1a** and **1b**

	ΔG
Oxalate-1a	0.0
MC1a	−2.6
TS1a	27.4
IN1a	8.0
TS2a	21.5
MC2a	−10.2
Oxalate-1b	0.0
MC1b	−0.8
TS1b	30.7
IN1b	12.8
TS2b	27.3
MC2b	−3.7

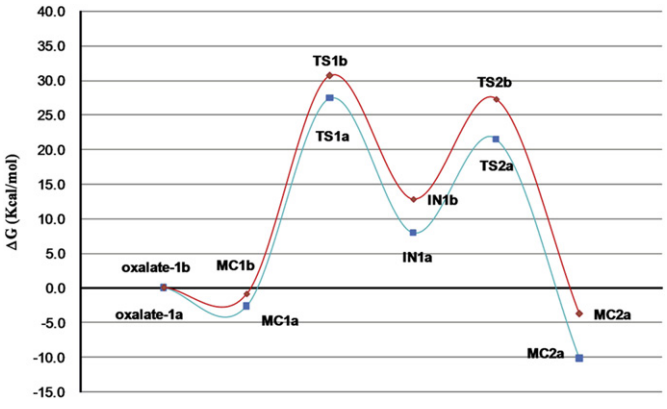


Fig. 2. Free energy profile (ΔG in kcal/mol), in vacuo, for the reaction of dimethyl oxalate with **1a** (in blue) and with **1b** (in red).

of the amino alcohol to the carbonyl group of the oxalate to yield the tetrahedral intermediate **IN1**. Extrusion of MeOH in the **TS2** leads to the intermediate **4**. It should be noted that in all transition states (**TS1** and **TS2**) there are intramolecular catalysis due to the hydroxyl group of the amino alcohol (see Fig. 3S in Supplementary data). Normally, transamination process requires the presence of a proton donor–acceptor (amine, alcohol or water) that catalyzes these reactions, through hydrogen bonds (HB), lowering the activation energy of TSs.[21] Without this catalytic effect, the transamination process requires high energy barriers. In this case the intramolecular catalysis is more favorable than usual intermolecular catalysis,[21] due to entropic factors.

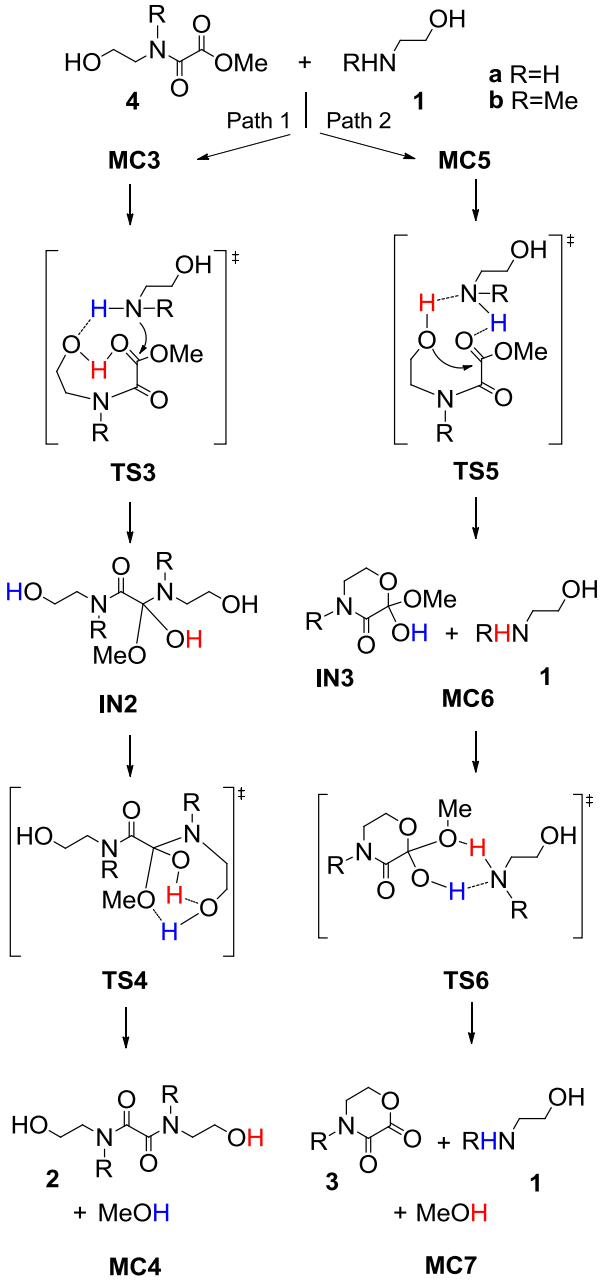
The conversion of the amino alcohol **1a** into the corresponding intermediate **4a** (see Table 2 and Fig. 2) has an activation free energy of 27.4 kcal/mol (**TS1a**). The initial intermolecular attack of the amine (**TS1a**), to give the tetrahedral intermediate **IN1a**, is the rate determining step of the process, being more energetic than the posterior extrusion of MeOH (21.5 kcal/mol, **TS2a**). Overall, the conversion of **1a** into **4a** is favored by 10.2 kcal/mol (see **MC2a**). It should be noted that the intramolecular catalysis, due to the hydroxyl group, reduces the activation energy of the process in about 11 kcal/mol. For example, the TS in the reaction of methyl amine with the dimethyl oxalate (without the catalytic effect of hydroxyl), has an activation energy (ΔE) of 35.1 kcal/mol (see Fig. 5S and Table 1S in Supplementary data).

The energy results for the conversion of **1b** in **4b** show a significant increase in the free energy of all TSs with respect to the equivalent TSs in the case of the amino alcohol **1a**. This may be due to steric interaction exerted by the additional methyl group (N–Me).

*2.2.2. Kinetic study: conversion of **4** into the oxalamide **2** and morpholinedione **3**.* The suggested mechanism for the conversion of the intermediate **4** into the oxalamide **2** and morpholindione **3** is presented in Scheme 3. All calculations were initially performed in vacuo. These steps determine the final products to be obtained (**2** or **3**). Therefore, to obtain more accurate results, calculations were also performed in toluene and ethanol (single point calculation).[22] In this case the study of the possible TSs is very complex due to the possibility of HB between hydroxyl and amino groups among themselves and with other functional groups present in the structures. After a careful research we only show, in order to simplify, the most stable TSs found (see Fig. 6S in Supplementary data). The free energies of the species are in Table 3, Fig. 3, and Fig. 4.

Conversion of intermediate **4** into linear oxalamide **2** is a transamination process similar to that discussed for the transformation of amino alcohol **1** into **4**. In this reaction pathway (Path 1 in Scheme 3), after the formation of a molecular complex (**MC3**), intermediate **4** is converted into oxalamide **2** through **TS3**, the tetrahedral intermediate **IN2** and **TS4**. **TS3** corresponds to the intermolecular attack of the amino group of the amino alcohol **1** to the carbonyl group of the ester moiety of **4** to yield the tetrahedral intermediate **IN2**. In this transition state (**TS3a** and **TS3b** in Fig. 6S in Supplementary data) there is intramolecular catalysis due to the hydroxyl group present in **4** and also an additional HB between this hydroxyl and the hydroxyl group of the amino alcohol **1**. Extrusion of MeOH in the intermediate **IN2** through **TS4** leads to the final oxalamide **2**. In this TS (**TS4a** and **TS4b** in Fig. 6S in Supplementary data), intramolecular catalysis is due to the hydroxyl group of the incoming amino alcohol.

For the conversion of intermediate **4** into cyclic morpholine-2,3-dione **3** we have investigated the reaction pathway 2 (Path 2 in Scheme 3) through **MC5**, **TS5**, **IN3** (actually, the molecular complex between **IN3** and **1**) and **TS6**. Throughout this process, the amino alcohol **1** acts as proton donor–acceptor. In the **TS5** (see **TS5a** and **TS5b** in Fig. 6S in Supplementary data) the intramolecular attack of the hydroxyl group of the amide moiety of **4** to the carbonyl group



Scheme 3. Mechanism for the conversion of the intermediate **4** into the oxalamide **2** and morpholinedione **3**.

of the ester moiety of **4** to yield the tetrahedral intermediate **IN3**, is catalyzed by amino group of the amino alcohol **1** yielding the tetrahedral intermediate **IN3**. Similarly, the extrusion of MeOH in the reaction intermediate **IN3**, through the **TS6** (see **TS6a** and **TS6b** in Fig. 6S in Supplementary data) is also catalyzed by the amino group of **1** giving the morpholine-2,3-dione **3**.

As it can be seen in Table 3 and Fig. 3, the conversion of the intermediate **4a** into oxalamide **2a** (Path 1 in Scheme 3), in vacuo, has an activation free energy of 29.2 kcal/mol (**TS3a**). In this case, the initial intermolecular attack of the amine group (**TS3a**) is the rate determining step of the process, being more energetic than the posterior extrusion of MeOH (23.1 kcal/mol, **TS4a**). The formation of the oxalamide **2a** (actually, the molecular complex **MC4** between **2a** and MeOH) is an exergonic process in −9.9 kcal/mol.

On the other hand, the conversion of the intermediate **4a** into cyclic morpholine-2,3-dione **3a** (Path 2 in Scheme 3), in vacuo,

Table 3
B3LYP/6-31G** relative free energies (ΔG, in kcal/mol), in vacuo in toluene and in ethanol, of the stationary points involved in the reaction of **4a** and **4b** with **1a** and **1b**, respectively

	ΔG (vacuo)	ΔG (toluene)	ΔG (ethanol)
4a–1a	0.0	0.0	0.0
MC3a	5.0	2.5	0.9
TS3a	29.2	26.6	24.7
IN2a	19.6	17.2	15.7
TS4a	23.1	20.6	18.9
MC4a	−9.9	−12.4	−14.1
MC5a	2.7	−1.4	−4.1
TS5a	27.7	22.4	18.6
MC6a	6.3	4.6	2.1
TS6a	25.0	20.2	16.5
MC7a	2.7	−0.9	−3.1
4b–1b	0.0	0.0	0.0
MC3b	−2.9	−1.2	−3.9
TS3b	27.5	28.9	26.0
IN2b	19.9	21.4	19.5
TS4b	29.6	30.7	28.8
MC4b	−3.9	−3.7	−6.6
MC5b	0.7	0.5	−3.0
TS5b	21.8	22.7	18.7
MC6b	4.4	4.1	−0.4
TS6b	19.1	18.1	14.3
MC7b	−2.4	−2.3	−5.5

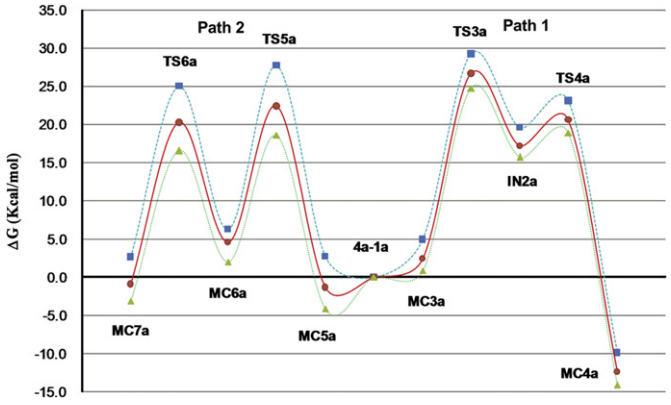


Fig. 3. Free energy profile (ΔG in kcal/mol), for the reaction of **4a** with **1a**, in vacuo (in blue) in toluene (in red) and in ethanol (in green).

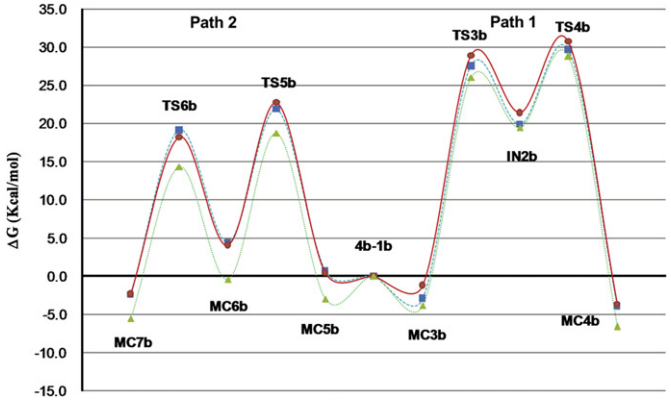


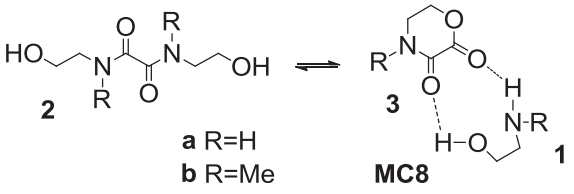
Fig. 4. Free energy profile (ΔG in kcal/mol), for the reaction of **4b** with **1b**, in vacuo (in blue) in toluene (in red) and in ethanol (in green).

going through **TS5a** (27.7 kcal/mol) and **TS6a** (25.0 kcal/mol), has activation free energy of 27.7 kcal/mol (**TS5a**). The initial intermolecular attack of the hydroxyl group of the amide moiety of **4a** to the carbonyl group of the ester moiety of **4a** is the rate determining step of the process, being more energetic than the posterior extrusion of MeOH. In this case, the overall process is slightly endergonic (2.7 kcal/mol, **MC7a**). Due to the polar nature of most of the species involved in the conversion of **4a** into **2a** and **3a**, the inclusion of the solvent (toluene or ethanol) causes a decrease in the energy of the species. This effect is more pronounced with the use of a more polar solvent, such as ethanol. The result is a decrease in the energy profile of the reaction (all overall processes become exergonic), but the energy difference between **TS3a** and **TS5a** does not substantially change.

The transformation of the intermediate **4b** into oxalamide **2b** and morpholine-2,3-dione **3b** shows similarities and differences with respect to the conversion of **4a** into **2a** and **3a**. The most notable data is the increase of the free energy barrier through the pathway 1. It is due to the increased energy of the **TS4b**, which becomes the limiting step of this process. This increased energy of **TS4b** with respect to **TS4a** is easily explainable analyzing the geometry of these transition states (Fig. 6S in Supplementary data). **TS4a** is stabilized with two five-membered rings formed by hydrogen bonding, N–H···O=C, which allows the flat arrangement of the oxalamide group.[14a] In the case of the **TS4b** the presence of N–Me prevents this option and produces a considerable increase in energy. The inclusion of solvent effect causes less variation in the energy of the species, possibly due to lower polarity of the compounds with the N–Me group. In fact there is very little variation between toluene and vacuo. Only in ethanol there is a clear decrease of the energy profile.

These results (Path 2 lower energy than Path 1) indicate that if the reaction had a kinetic control, the major product would be the cyclic morpholine-2,3-dione **3**. In the experimental reaction is obtained mostly the linear oxalamide **2** (see Table 1). This suggests that these reactions are not kinetically controlled, there must be an equilibrium between all species and therefore it must follow a thermodynamic control. To explore the relative stability of the reaction products, we performed a thermodynamic study. Experimental studies were also conducted to support this hypothesis.

2.2.3. Thermodynamic study. For thermodynamic study, we considered the equilibrium represented in Scheme 4. In this scheme the linear oxalamide **2** is in equilibrium with the complex formed between the cyclic morpholine-2,3-dione **3** and the amino alcohol **1** (**MC8**). For each specie (**2a**, **2b**, **MC8a**, and **MC8b**), we conducted a detailed conformational study, with full minimization at each of the solvents used (toluene and ethanol). Conformational study of oxalamides **2** is very complex and has been published previously.[14a] Free energies corresponding to the most stable conformers found for **2** and **MC8** are collected in Table 4. The molecular complexes **MC8a** and **MC8b**, are stabilized by a double HB. These HB occur between the hydroxyl group and amino group of the amino alcohol **1** and the oxygen of the carbonyl groups of the cyclic morpholinedione **3** (see Fig. 9S in Supplementary data).



Scheme 4. Equilibrium between **2** and **MC8**.

The results for the equilibrium **2a**···**MC8a**, show a large difference in free energy. The oxalamide **2a** is much more stable than the

Table 4
B3LYP/6-31G** relative free energies (ΔG, in kcal/mol), in toluene and in ethanol, of the compounds **2** and molecular complexes **MC8**

	ΔG (toluene)	ΔG (ethanol)
2a	0.0	0.0
MC8a	14.0	13.1
2b	0.0	0.0
MC8b	5.2	1.9

MC8a, both in toluene and ethanol, with a value of 14.0 kcal/mol and 13.1 kcal/mol, respectively. These energy values clearly indicate that in the equilibrium the only observable product would be the linear oxalamide **2a**, according to experimental results (see Table 1). The presence of substituents other than hydrogen on the carbons adjacent to the hydroxyl and amino groups (**2c**, **2d**, and **2h**) may vary slightly these energetic results, but hardly enough to approximate the difference in energy between **2** and **MC8**.

We conclude that in the reaction of primary β-amino alcohols with dialkyl oxalates, linear oxalamides are obtained as the compounds of reaction, regardless of solvent used. With this type of amino alcohols should not be detected the presence of cyclic morpholin-2,3-diones.

It should be noted that in the reaction of amino alcohol **1h** with diethyl oxalate, the presence of the intermediate **4h** (see Table 1) may be due to its high stability. In this case the stability of this intermediate should be similar to that of the final linear oxalamide **2h**. In fact, using ethanol as a solvent there is a shift of equilibrium toward the aforementioned intermediate **4h**.

In the case of **2b**···**MC8b** equilibrium, the differences in free energy between **2b** and **MC8b** are significantly reduced. By using toluene as a solvent, **2b** remains as the more stable product in 5.2 kcal/mol, while in ethanol the difference in free energy is only 1.9 kcal/mol. According to these results, the use of ethanol as solvent increases the proportion of the cyclic compound **3b**. The energy difference, in toluene, between **2b** and **MC8b** (5.2 kcal/mol) does not allow a sufficient concentration of **MC8b** in the equilibrium and therefore there is no observable morpholine-2,3-diones **3b** in the reaction between amino alcohol **1b** and diethyl oxalate. However, this difference in ethanol is only 1.9 kcal/mol, this allows obtaining a small amount of **3b** in the reaction between amino alcohol **1b** and diethyl oxalate, according to experimental results (see Table 1). In this situation, changes in the substituents of the *N*-alkyl β-amino alcohols **1**, as well as the reaction conditions, can lead to different results depending on the relative stability between the linear oxalamide **2** and the **MC8**. For example (see Table 1), in toluene, there is a 3% and 4% of the corresponding cyclic compounds **3f** and **3g**, while in ethanol there is a 4% and 12% of **3b** and **3g**, respectively.

The different behavior between the primary β-amino alcohols and *N*-methyl β-amino alcohols is due to the difference in stability of linear disubstituted oxalamides (**2a**, **2c**, **2e**, and **2h**) with respect to linear tetrasubstituted oxalamides (**2b**, **2d**, **2f**, and **2g**). In fact, by observing the **MC8a** and **MC8b** (Fig. 9S in Supplementary data), the presence of the *N*-methyl group in the **MC8b** almost does not affect this MC with respect to the **MC8a** neither by steric interaction nor electronic factors. However, as mentioned above for **TS4a** and **TS4b**, the linear disubstituted oxalamides (see **2a** in Fig. 9S in Supplementary data) are stabilized with two five-membered rings formed by hydrogen bonding, N–H···O=C, which allows the flat arrangement of the oxalamide group.[14a] In the linear tetrasubstituted oxalamides (see **2b** in Fig. 9S in Supplementary data) the presence of N–Me prevent this option and produces a considerable increase in energy. In consequence, the energy of **2b** is closer to the energy of **MC8b**.

2.3. Additional experimental evidences

With the aim of supporting the suggested thermodynamic control in the reaction of β-amino alcohols with dialkyl oxalates, we have carried out additional experimental assays. Compound **1a** was selected as an example of primary β-amino alcohol and compounds **1b**, **1d**, **1f**, and **1g** were selected as examples of *N*-substituted β-amino alcohols. To this end, we have changed the proportions of the reactants to 1 equiv of amino alcohol and 1 equiv of oxalate. These proportions are supposed to favor the formation of cyclic morpholine-2,3-diones **3**, and therefore it can expect an increase in the proportion of these compounds. The results are shown in Table 5.

Table 5
Reaction of 1 equiv of β-amino alcohols **1** with 1 equiv of diethyl oxalate in toluene or in ethanol

Amino alcohol (solvent)	Products	Yield (%) [a]
1a (Ethanol)	**2a**	93
1b (Toluene)	**2b**	91
	3b	7
1b (Ethanol)	**2b**	53
	3b	43
1d (Ethanol)	**2d**	85
	3d	10
1f (Toluene)	**2f**	86
	3f	11
1g (Ethanol)	**2g**	56
	3g	40

[a] Yield (%) from ^{1}H NMR of the crude of reaction.

As expected, in the reaction of the primary amino alcohol **1a** with oxalate in ethanol (the most favorable reaction conditions), we obtained only the linear compound **2a** without the presence of cyclic compound **3a**. However, in the reaction of *N*-substituted amino alcohols (**1b**, **1d**, **1f**, and **1g**), both in toluene and ethanol, it was observed an increase toward the cyclic morpholine-2,3-diones **3** with respect to the corresponding reaction carried out in proportion 2:1 (see Table 1). In reactions that previously showed no cyclic compounds, for example, **1b** in toluene or **1d** in ethanol, it can see now these compounds. Again, the use of ethanol instead of toluene favors the formation of cyclic morpholine-2,3-diones **3**. These results clearly confirm the thermodynamic control of these reactions.

As previously noted, in the transamination process of dialkyl oxalate into oxamidic ester intermediate **4**, there is intramolecular catalysis due to the hydroxyl group of the amino alcohol **1** (see Scheme 2). Also, in the conversion of the intermediate **4** into the oxalamide **2** (see Scheme 3) there is intramolecular catalysis due to the hydroxyl group present in **4** (see **TS3**) or due to the hydroxyl group of the incoming amino alcohol (see **TS4**). Finally, in the conversion of the intermediate **4** into the morpholinedione **3** (see Scheme 3, **TS5** and **TS6**) the amino alcohol **1** acts as a catalyst. As a result, the energy barriers for the reactions and also for the interconversion between species are quite low. We have already established that the reaction follows a thermodynamic control and therefore these energy barriers do not influence the proportion of the final products of reaction, but in the overall speed of all processes. In view of the energy values calculated, the rate of reaction should occur much more quickly than expected. At experimental level, it is known that secondary amines (without the hydroxyl group) react only slowly and incompletely with diethyl oxalate.[11] Also experimental conditions, commonly used, include long reaction time, at room temperature, or reflux in the solvents used.

In order to verify the acceleration of the reactions, which involves an amino alcohol, the reaction of dimethyl oxalate with

the amino alcohol **1b** (1:1 ratio) was carried out in a NMR tube. Deuterated methanol was used as solvent at 25 °C. ^{1}H and ^{13}C spectra were recorded after 30 min and after 24 h. The spectra recorded at 30 min showed a 6:4 ratio of compounds **2b** and **3b**, respectively (similar to the corresponding reaction in Table 5), as well as unreacted dimethyl oxalate. To obtain the linear compound **2b**, the consumption of 2 equiv of amino alcohol is required, thus leaving an excess of oxalate. As traces, are noted another product that could be the intermediate **4b**. The presence of starting amino alcohol **1b** was not detected. The spectra at 24 h were almost identical, demonstrating that the reaction had been completed in those 30 min. The addition of a new equivalent of amino alcohol **1b**, has produced a disturbance of equilibrium and therefore a change in the ratio of the products. In this case the major product of the reaction was linear compound **2b** with a ratio above 95% (similar to the corresponding reaction in Table 1).

3. Conclusions

The reaction of β-amino alcohols with dialkyl oxalate can lead to the production of linear oxalamides and cyclic morpholine-2,3-diones. Reaction of primary β-amino alcohols with dialkyl oxalate afforded the corresponding linear disubstituted oxalamides regardless of the solvent used (toluene or ethanol), the ratio of amino alcohol and dialkyl oxalate (2:1 or 1:1), and the presence of substituents other than hydrogen on the carbons adjacent to the hydroxyl and amino groups. When using *N*-substituted β-amino alcohols in a 2:1 ratio amino alcohol:oxalate the major product is the corresponding linear tetrasubstituted oxalamide, but in some cases there is a small amount of cyclic morpholine-2,3-dione. In a 1:1 ratio the cyclic morpholine-2,3-dione product increases, being greater with the use of ethanol as a solvent.

The possible mechanism for the reaction of β-amino alcohols with the dialkyl oxalate to yield the final linear oxalamides or the cyclic morpholine-2,3-diones, has been investigated in vacuo and in solvent (toluene and ethanol), using DFT methods at the B3LYP/6-31G** computational level. Formation of linear oxalamides or cyclic morpholinediones shares a common oxamidic ester intermediate. The formation of this intermediate is produced by intermolecular nucleophilic substitution of an alkoxide of the dialkyl oxalate by the amino group of the amino alcohol in a two-steps process. This intermediate is converted into oxalamide through another two-steps intermolecular nucleophilic substitution of the alkoxide remainder with a second molecule of amino alcohol. Cyclic morpholine-2,3-diones arises from the intramolecular attack of the hydroxyl group of the intermediate to the carbonyl group of the ester moiety with extrusion of alkoxide group. In all steps, there is a strong catalytic effect produced by amino or hydroxyl group of the amino alcohol and thus the energy barriers are quite low. These theoretical results indicate that these reactions are not kinetically controlled, there is an equilibrium between all species and therefore follow a thermodynamic control.

The different behavior between the primary β-amino alcohols and *N*-methyl β-amino alcohols is due to the difference in stability of linear disubstituted oxalamides with respect to linear tetrasubstituted oxalamides. The linear disubstituted oxalamides are stabilized with two five-membered rings formed by hydrogen bonding, N–H···O=C, which allows the flat arrangement of the oxalamide group, and are much more stable than their corresponding morpholine-2,3-diones. In the linear tetrasubstituted oxalamides the presence of N–Me prevent this option and produce a considerable increase in energy. In consequence, the energy of tetrasubstituted oxalamides is closer to the energy of the corresponding morpholine-2,3-diones.

4. Experimental section

4.1. Computational methods

All calculations were carried out with the Gaussian 03 suite of programs.[23] Density functional theory[24] calculations (DFT) have carried out using the B3LYP[25] exchange-correlation functionals, together with the standard 6-31G** basis set.[26] In the previous conformational study on this type of molecules, this basis set led to us concordant results between theoretical calculations and experimental results.[14a] Due to the large amount of calculations carried out, a higher level of calculation (e.g., 6-311++G**) is not considered necessary. Since the mechanism involves polar species the inclusion of solvent effects have been considered by using a relatively simple self-consistent reaction field (SCRF) method[27] based on the polarizable continuum model (PCM) of Tomasi's group.[28] As indicated in the text, calculations have been made with single point or total minimization in the solvents used (toluene and ethanol).

4.2. General

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. Solvents were distilled prior to use. Thin layer chromatography was performed on plates precoated with silica gel Si60-F254 (Merck, Darmstadt, Germany). Column chromatography was carried out with silica gel Si60, mesh size 0.040–0.063 mm (Merck, Darmstadt, Germany). Melting points were determined with a Sanyo–Gallencamp capillary apparatus and are uncorrected. IR spectra were recorded on a Jasco FTIR 5300 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance DRX 300 MHz (300 and 75 MHz, respectively) spectrometer, in DMSO-d_6 and in $CDCl_3$ solutions. Chemical shifts were recorded in parts per million (ppm), downfield from internal Me_4Si. The coupling constants *J* are given in Hz. The one-bond multiplicity of carbon atoms was determined by DEPT experiments. High-resolution mass spectral data were obtained on a VG Autospec, TRIO 1000 (Fisons) instrument. Electron impact (EI) or Fast Atom Bombardment (FAB) at 70 eV were used as ionization mode in mass spectra. The structure of all the compounds was determined by analytical and spectroscopic methods, and by comparison with data of the compounds reported in literature.

4.3. General procedures for the preparation of oxalamides (2), morpholine-2,3-diones (3)

Method A: Diethyl oxalate (0.5 mmol) was added dropwise to a stirred solution of the appropriate amino alcohol **1** (1 mmol) in toluene or ethanol (4 ml). The mixture was stirred at rt for 24 h. If a solid appears was filtered under reduced pressure and analyzed; the filtrate liquid was concentrated to dryness and analyzed by ^{1}H NMR. When not precipitated, the crude reaction mixture was concentrated to dryness and analyzed by ^{1}H NMR. To obtain analytical information the products were purified by column chromatography.

Method B: Diethyl oxalate (1 mmol) was added dropwise to a solution of the appropriate amino alcohol **1** (1 mmol) in toluene or ethanol (4 ml). The mixture was stirred at rt for 24 h, concentrated to dryness, and the crude reaction mixture was analyzed by ^{1}H NMR.

*4.3.1. Starting β-amino alcohol: 2-aminoethanol (**1a**). Method A* (Toluene): *N,N'-bis-(2-hydroxy-ethyl)-oxalamide* (**2a**)[14a,15] precipitated (94%). *Method A* (Ethanol): **2a** precipitated (76%)+**2a** (19%) in the filtrate liquid.

Method B (Ethanol): **2a** (93%).

*4.3.2. Starting β-amino alcohol: N-methylethanolamine (**1b**). Method A* (Toluene): *N, N'-bis-(2-hydroxy-ethyl)-N,N'-dimethyl-oxalamide* (**2b**)[14a] (96%) in the crude reaction mixture.

Method A (Ethanol): a mixture of **2b** (90%) and *4-methyl-morpholine-2,3-dione* (**3b**)[19] (4%) in the crude reaction mixture.

Method B (Toluene): a mixture of **2b** (91%) and **3b** (7%).

Method B (Ethanol): a mixture of **2b** (53%) and **3b** (43%).

*4.3.3. Starting β-amino alcohol: 2-amino-1-phenylethanol (**1c**). Method A* (Toluene): *N,N'-bis-(2-hydroxy-2-phenyl-ethyl)-oxalamide* (**2c**) precipitated (96%).

Method A (Ethanol): **2c** precipitated (77%)+**2c** (18%) in the filtrate liquid.

2c: White solid; mp 186–187 °C. IR (KBr) ν_{max}: 3302; 1649; 1537 cm^{-1} ^1H NMR (300 MHz, DMSO-d_6):δ=3.23–3.34 (m, 4H, 2× CH_2–N), 4.73 (m, 2H, 2× CH–O), 5.58 (bs, 2H, 2× OH, exchangeable with D_2O), 7.23–7.34 (m, 10H, 2× C_6H_5), 8.51 (t, ^3J=6.0 Hz, 2H, 2× NH, exchangeable with D_2O) ppm ^{13}C NMR (75.4 MHz, DMSO-d_6):δ=47.23 (t), 70.99(d), 126.31 (d), 127.51 (d), 128.42 (d), 143.54 (s), 160.07 (s) ppm. HMRS (FAB) calcd for $C_{18}H_{19}N_2O_3$ $[M-OH]^+$ 311.1395; found: 311.1387.

*4.3.4. Starting β-amino alcohol: 2-(methylamino)-1-phenylethanol (**1d**). Method A* (Toluene): *N,N'-bis-(2-hydroxy-2-phenyl-ethyl)-N,N'-dimethyl-oxalamide* (**2d**) precipitated (84%)+**2d** (5%) in the filtrate liquid.

Method A (Ethanol): oxalamide **2d** (92%) in the crude reaction mixture.

Method B (Ethanol): a mixture of **2d** (85%) and *4-methyl-6-phenylmorpholine-2,3-dione* (**3d**).[19]

2d: White solid; mp 132–133 °C. IR (KBr) ν_{max}: 3476, 3369, 1651, 1631 cm^{-1} ^1H NMR (300 MHz, $CDCl_3$):δ=2.80–3.00 (several s, N–CH_3), 3.10–5.30 (several bs, OH), 3.15–3.75 (m, CH_2–N), 4.7–5.30 (m, CH–O), 7.29 (m, C_6H_5) ppm ^{13}C NMR (75.4 MHz, Cl_3CD):δ=32.71, 32.82, 33.15, 37.0. 37.1, 37.9 (CH_3–N), 54.84, 55.40, 57.46, 57.53, 57.57, 57.62, (CH_2–N), 70.26, 70.66, 70.96, 71.10, 71.61, 71.84, 72.13 (CH–O), 125.86, 125.93, 125.94, 126.02, 126.09, 128.05, 128.69, 128.72, 128.78, 128.84, 141.46, 141.47, 141.74, 141.81, 141.86, 142.01, 142.13 (C_6H_5), 165.22, 165.48, 165.78, 166.11, 166.25, 166.41 (C=O) ppm. HRMS (FAB) calcd for $C_{20}H_{25}N_2O_4$ $[M+H]^+$ 357.1814; found 357.1811.

*4.3.5. Starting β-amino alcohol: (2R,3R)-3-amino-3-phenylpropane-1,2-diol (**1e**). Method A* (Toluene): *N,N'-bis-[(1R, 2R)2,3-dihydroxy-1-phenylpropyl]oxalamide* (**2e**),[14b] precipitated (96%).

Method A (Ethanol): **2e** precipitated (76%)+**2e** (19%) in the filtrate liquid.

*4.3.6. Starting β-amino alcohol: (1S,2R)-(+)-ephedrine (**1f**). Method A* (Toluene): *N,N'-bis-[(1S,2R)-(+)-ephedrine]oxalamide* (**2f**) (90%) precipitated+a mixture of (**2f**) (3%): (*5R,6S*)-*4,5-dimethyl-6-phenylmorpholine-2,3-dione* (**3f**)[19] (3%) in the filtrate liquid.

Method A (Ethanol): a mixture of **2f** (95%) and **3f** (traces) in the reaction crude mixture.

Method B (Toluene): a mixture **2f** (86%) and **3f** (11%).

2f: White solid, mp. 146–147 °C. IR (KBr) ν_{max}: 3404, 1620, 1599 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=0.91, 1.00 (2d, CH_3–C), 2.62, 2.71, 2.86 (3s, CH_3–N), 3.33, 3.98, 4.37 (m, CH–N), 4.70, 4.88, 5.17 (3d, CH–O), 7.18–7.41 (m, C_6H_5) ppm ^{13}C NMR (75.4 MHz, DMSO-d_6): δ=9.17, 10.50, 11.28 (CH_3–C), 26.53, 30.60, 31.31 (CH_3–N), 52.59, 57.48, 59.26 (CH–N), 69.68, 74.61, 75.96 (CH–O), 125.88, 126.03, 126.24, 127.35, 127.86, 127.98, 128.25, 141.36, 143.78, 143.90 (C_6H_5), 168.77, 169.08, 169.98, 170.32 (C=O) ppm. HMRS (FAB) calcd for $C_{22}H_{29}N_2O_4$ $[M+H]^+$ 385.2127; found 385.2137.

*4.3.7. Starting β-amino alcohol: (1S,2S)-(+)-pseudoephedrine (**1g**). Method A* (Toluene): *N,N'-bis-[(1S,2S)-(+)-pseudoephedrine] oxalamide* (**2g**) (76%) precipitated+a mixture of **2g** (12%): (*5S,6S*)-*4,5-dimethyl-6-phenylmorpholine-2,3-dione* (**3g**) (4%) in the filtrate liquid.

Method B (Ethanol): a mixture of **2g** (56%) and **3g** (40%).

2g: White solid; mp 174–175 °C. IR (KBr) ν_{max}: 3472, 3377, 1643, 1620 cm^{-1} ^1H NMR (300 MHz, CD_3OD):δ=0.85–1.00 (several d, CH_3–C), 2.65–3.00 (several s, CH_3–N), 3.66, 4.45 (2 m, CH–N), 4.40–4.60 (m, CH–O), 7.10–7.40 (m,C_6H_5) ppm ^{13}C NMR (75.4 MHz, CD_3OD): δ=14.68, 16.18 (CH_3–C), 26.68, 31.69 (CH_3–N), 61.92 (CH–N), 75.85, 76.03 (CH–O), 128.35, 128.56, 129.38, 129.86, 129.96, 143.97 (C_6H_5), 166.26, 166.87 (C=O) ppm. HMRS (EI) calcd for $C_{22}H_{29}N_2O_4$ $[M+H]^+$ 385.2127; found 385.2130.

3g: White solid; mp 94–96 °C. IR (KBr) ν_{max}: 3456, 1765, 1689 cm^{-1} ^1H NMR (300 MHz, $CDCl_3$):δ=1.41 (d, ^3J=6.8 Hz, 3H, CH_3–C), 2.92 (s, 3H, CH_3–N), 3.89 (m, 1H, CH–N), 5.30 (d, ^3J=4.0 Hz, 1H, CH–O), 7.20–7.32 (m, 5H, C_6H_5) ppm ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=17.77 (q, CH_3–C), 32.98 (q, CH_3–N), 57.46 (d, CH–N), 81.82 (d, CH–O), 126.11, 129.37, 129.46, 136.12 (C_6H_5), 153.89 (s, N–C=O), 156.70 (s, O–C=O) ppm. HMRS (EI) calcd for $C_{12}H_{13}NO_3$ $[M]^+$ 219.0895; found 219.0898.

*4.3.8. Starting β-amino alcohol: (1R,2S)-(−)-norephedrine (**1h**). Method A* (Toluene): *N,N'-bis-[(1R,2S)-(−)-norephedrine]oxalamide* (**2h**)[16] precipitated (88%)+a mixture of **2h** (3%) and *N-[(1R,2S)-(2-Hydroxy-1-methyl-2-phenyl-ethyl)]oxalamic acid ethyl ester* (**4h**)[17] (6%).

Method A (Ethanol): **2h** precipitated (13%)+a mixture of **2h** (7%): **4h** (65%) in the filtrate liquid.

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Supplementary data

Figs. 1S–10S, Tables 1S–4S, and Scheme 1S. ^1H NMR and ^{13}C NMR spectra of **2c**, **2d**, **2f**, **2g**, and **3g**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.09.067. These data include MOL files and InChiKeys of the most important compounds described in this article.

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