

## Theoretical Evidence for Pyramidalized Bicyclic Serine Enolates in Highly Diastereoselective Alkylations

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**Abstract:** A new chiral serine equivalent and its enantiomer have been synthesized from (*S*)- and (*R*)-*N*-Boc-serine methyl esters (Boc: *tert*-butyloxycarbonyl). The use of these compounds as chiral building blocks has been demonstrated in the synthesis of  $\alpha$ -alkyl  $\alpha$ -amino acids by diastereoselective po-

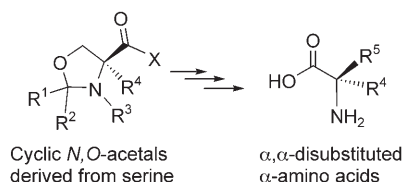
tassium enolate alkylation reactions and subsequent acid hydrolyses. Theoretical studies were performed to eluci-

date the stereochemical outcome of both the formation of five-membered cyclic *N,O*-acetals and the subsequent alkylation process, which occurs with total retention of configuration. This feature could be explained in terms of the high degree of pyramidalization of enolate intermediates.

**Keywords:** ab initio calculations • alkylation • amino acids • asymmetric synthesis • carbanions

### Introduction

In the course of our studies towards synthetic routes for  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acids based on the use of five-membered cyclic *N,O*-acetals,<sup>[1]</sup> we became interested in diastereoselective alkylations of chiral serine equivalents (Scheme 1).



Scheme 1. Five-membered cyclic *N,O*-acetals as chiral building blocks.

In this context, five-membered cyclic *N,O*-acetals derived from *L*-serine or *L*-serinal (i.e., Garner aldehyde) have been extensively used as three-carbon building blocks in organic

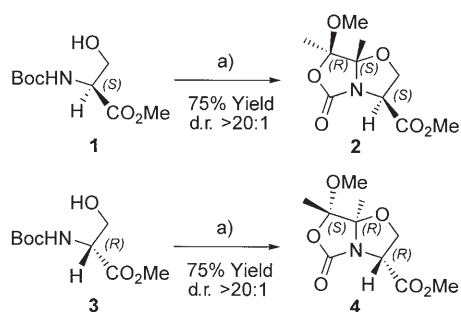
synthesis.<sup>[2]</sup> Diastereoselective methylation of an *N,O*-acetal serine derivative incorporating a new stereogenic center at the acetal carbon atom has recently been described.<sup>[2g]</sup> However, due to the propensity of these materials to polymerize, racemize, and form hydrates, the compounds must be freshly prepared, and their storage is not recommended. An alternative approach to prepare stable and readily available derivatives is therefore needed to overcome these problems, particularly in terms of scale-up. With this aim in mind, we envisioned the design of other, more stable, chiral, five-membered cyclic *N,O*-acetal serine derivatives by incorporating a new ring in the structure; it was envisioned that this ring could also favor diastereoselectivity in subsequent alkylations by means of increased rigidity.

### Results and Discussion

**Synthesis of bicyclic *N,O*-acetal serine derivatives as chiral building blocks:** We first treated 2,3-dimethoxybutadiene in the presence of a catalytic amount of triphenylphosphine hydrobromide<sup>[3]</sup> with commercially available *N*-Boc-*L*-serine methyl ester **1** at room temperature. Building block **2** was obtained in 11% yield as the only product from a complex reaction mixture (Scheme 2). In an effort to increase this yield, we investigated the reaction of 2,2,3,3-tetramethoxybutane<sup>[4]</sup> with protected serine **1** in the presence of *p*-toluenesulfonic acid in refluxing toluene. This again gave chiral bicyclic *N,O*-acetal **2**, but in this case the yield, on a multi-gram scale, was 75% under the same conditions. This com-

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Scheme 2. Synthesis of chiral bicyclic serine equivalents **2** and **4**. Reagents and conditions: a) 2,2,3,3-Tetramethoxybutane, *p*-TsOH·H<sub>2</sub>O, toluene, reflux.

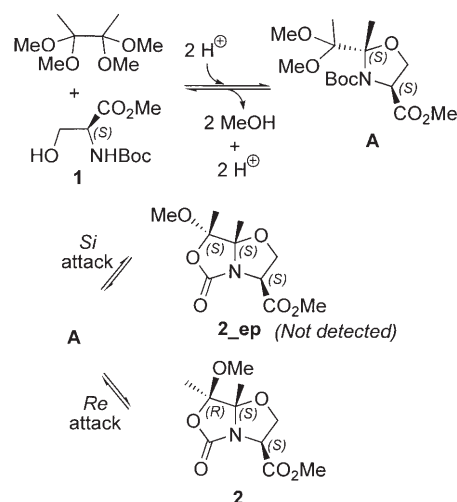
pound was obtained as a single diastereomer, as determined by <sup>1</sup>H NMR spectroscopy (d.r. >20:1).<sup>[5]</sup> This bicyclic structure was assessed by complete NMR analysis, including NOE experiments.

Starting from *N*-Boc-*D*-serine methyl ester **3**, this protocol allows the preparation of bicyclic *N,O*-acetal **4**, which is the enantiomer of **2**, as demonstrated by NMR spectroscopy and comparison of the optical activities of the two compounds (see the Supporting Information). This finding is not trivial and implies complete control of stereoselectivity throughout the whole multistep process. It is noteworthy that the application of a similar synthetic methodology to other alkoxy-carbonylamino alcohols<sup>[2f,6]</sup> proceeds via the formation of six-membered cyclic butane-2,3-diacetals.

**Mechanism of formation of building block 2:** The proposed mechanism for this reaction is depicted in Scheme 3 and involves the typical acid-catalyzed formation of *N,O*-acetals **A** starting from protected amino alcohols and acetalic compounds<sup>[2]</sup> as the first steps.

The final steps of the reaction are promoted by the well-known nucleophilic character of the *tert*-butyloxycarbonyl (Boc) group,<sup>[7,1c,e,f]</sup> which is able to trap the intermediate species generated by expelling the *tert*-butyl fragment, leading to stable bicyclic **2**. Considering the large number of equilibria involved in this reaction, we believe that irreversi-

**Abstract in Spanish:** *Se ha sintetizado un nuevo equivalente de serina quiral y su enantiómero a partir de los ésteres metílicos de (S)- o (R)-N-Boc-serina. Se ha demostrado su uso como excelentes building blocks quirales mediante la síntesis de varios α-alkil-α-aminoácidos, empleando reacciones de alquilación diastereoselectivas con enolatos de potasio y posterior hidrólisis ácida. Se han realizado estudios teóricos para elucidar el comportamiento estereoquímico tanto de la formación de los N,O-acetales cíclicos de cinco miembros como del posterior proceso de alquilación, transcurriendo éste con total retención de configuración. Esta característica podría explicarse atendiendo a una importante piramidalización en los enolatos intermedios.*



Scheme 3. Proposed mechanism for the formation of building block **2**.

ble participation of the Boc group can be regarded as the driving force for the global process. A significant piece of experimental evidence that supports this mechanism is that when the same reaction was carried out with benzyloxycarbonyl (Cbz)-protected methyl serinate instead of Boc-protected methyl serinate, bicyclic *N,O*-acetals were not isolated from the rather complex mixture obtained under the same conditions.

Generation of **2** and **4** with three stereogenic centers as single diastereomers necessarily involves a high level of diastereocontrol in all reaction steps. We observed that the configuration of the starting material governs the configuration of the final product. In this sense, when the enantiomer of the reacting serinate **1** (serinate **3**) was employed, the absolute configuration of all stereocenters was inverted in the final product **4**, as mentioned above.

To gain insight into this synthetic route, we carried out theoretical calculations employing DFT methods (see Computational Details). Due to the greater complexity of modeling the initial reaction steps, we centered our study on diastereoselective ring closure to give the five-membered *N,O*-acetalic species, promoted by the action of the Boc group.

The reactant in this final stage was considered to be mainly **A** on account of its greater thermodynamic stability compared to that of its epimer at the *N,O*-acetalic carbon atom (**A<sub>ep</sub>**, Figure 1). All calculated conformers of **A** are about 1 kcal mol<sup>-1</sup> lower in Gibbs free energy, which is in accordance with the diastereomeric ratio previously reported for the reaction of **1** with pivalaldehyde (3:1).<sup>[8]</sup> This situation is probably due to the more stable *trans* disposition of bulky groups in the five-membered ring.

Several approaches to the intramolecular attack of the Boc group on the remaining acetalic region were investigated, including the pure carbocationic form and others with pseudo-concerted loss of methanol. Unfortunately, none of the transition structures (TS) involved in these pathways could be located by the theoretical methods used in this work, and consequently “kinetic” information for this pro-

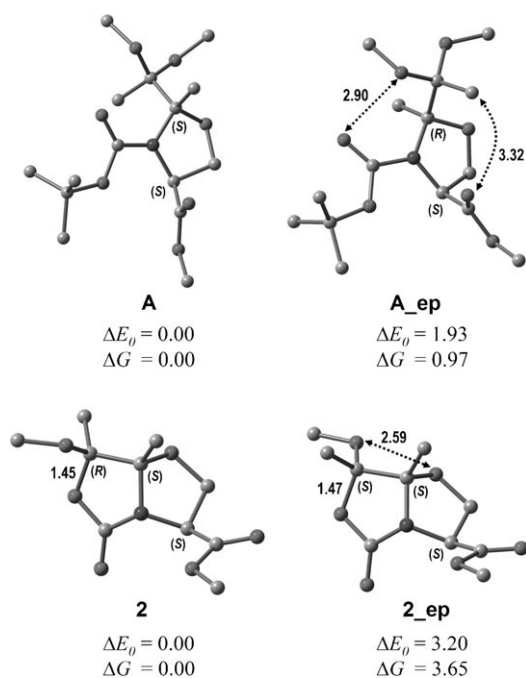


Figure 1. Calculated [B3LYP/6-31+G(d)] minimum-energy geometries of intermediate **A**, its epimer at the *N,O*-acetalic carbon atom **A\_ep**, bicycle **2** and its epimer at the *O,O*-acetalic carbon atom **2\_ep**. Relative energies are given in kcal mol<sup>-1</sup> and distances in Å.

cess could not be obtained. This problem is due to the extreme flatness of the potential-energy surface (PES) in the neighbourhood of the TS, which precludes convergence of the desired structures. Therefore, only the thermodynamic stabilities of the products could be evaluated. Several conformers of the bicycle **2** and its epimer **2\_ep** were calculated (see the Supporting Information and Figure 1). The structures with the experimentally observed distribution of stereocenters (*Re* attack) were found to be significantly more stable (by ca. 3–4 kcal mol<sup>-1</sup>) than their epimers at the *O,O*-acetalic carbon atom, and this led to the exclusive formation of compound **2**. This feature is mainly due to the lower steric congestion in the *trans* disposition of the acetalic methoxyl group and the *N,O*-acetalic oxygen atom in **2** with respect to its epimer **2\_ep**. Therefore, in the absence of more helpful experimental information, we propose thermodynamic control along the whole reaction profile, which leads to the most stable compound at the end of the global process.

**Diastereoselective alkylation of building block 2:** Given the easy access to chiral serine-derived building blocks **2** and **4**, and with the aim of assessing their use as precursors for the asymmetric synthesis of  $\alpha$ -alkyl  $\alpha$ -amino acids, we attempted the alkylation of these com-

pounds under standard conditions. Treatment of **2** with methyl triflate (MeOTf) at  $-78^\circ\text{C}$  in THF as solvent, followed by the addition of potassium hexamethyldisilazide (KHMDs), produced the methylated derivative as a single diastereomer (d.r. > 20:1).<sup>[5]</sup>

The reaction proceeds with high yield in a short time (5 min). For other less reactive alkyl groups or worse leaving groups (Table 1), the addition of four equivalents of hexa-

Table 1. Diastereoselective alkylation of building block **2**.

Entry	RX	HMPA (equiv)	Conversion <sup>[a]</sup>	<b>5a-d</b> / <b>6</b>	Product (yield [%]) <sup>[b]</sup>
1	MeOTf	0	100	57/10	<b>5a</b> <sup>[c]</sup> (85)
2	MeI	4	100	10/10	<b>5a</b> <sup>[c]</sup> (50)
3	EtOTf	4	80	70/10	<b>5b</b> <sup>[d]</sup> (70)
4	BnI	4	100	4.3/10	<b>5c</b> <sup>[c]</sup> (30)
5	AllylI	4	100	23/10	<b>5d</b> <sup>[d]</sup> (70)
6	none	0	100	–	<b>6</b> <sup>[c]</sup> (95)

[a] Determined by integration of the CH<sub>2</sub> signal in the <sup>1</sup>H NMR spectra. [b] Yield after column chromatography. [c] Stereochemistry predicted by NOE. [d] Stereochemistry determined by X-ray analysis.

methylphosphoramidate (HMPA) was required. The stereochemistry of some of the new compounds (**5b** and **5d**) was unambiguously determined by X-ray diffraction analysis<sup>[9]</sup> of single crystals obtained by slow evaporation of hexane/ethyl acetate (Figure 2). The bridgehead carbamate N atom is strongly pyramidalized in these compounds, and both five-membered rings are folded, in accordance with similar structures previously published.<sup>[10]</sup> In all cases, we detected the formation of a secondary product along with the alkylated compounds. This side product, which could be almost quantitatively obtained when an electrophile was not added, was found to be an acrylate generated by the well-known retro-*O*-Michael reaction involving the potassium enolate.<sup>[11]</sup>

**Mechanistic considerations on the stereochemical outcome of the alkylation process:** The stereochemical course of the

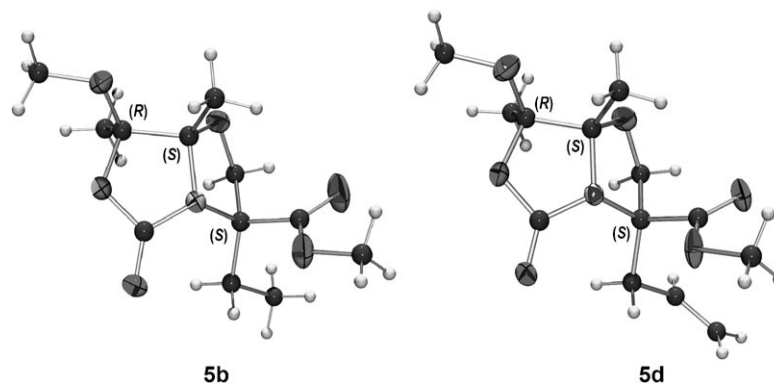


Figure 2. X-ray diffraction structures of the alkylation products **5b** and **5d**.

alkylation reaction involves a process with retention of configuration. To gain insight into the origin of this feature, we carried out a thorough theoretical study of all reaction channels accessible from the enolate of bicycle **2** (see Computational Details). The initial pathways to be evaluated were *C*-alkylation (**5a**), *O*-alkylation (although experimentally this was not detected) and retro-*O*-Michael reaction (**6**). Bromomethane was chosen as the alkylating agent in calculating the aforementioned pathways. The choice of this electrophile allowed us to study thoroughly the complex reaction scenario using a good level of theory while maintaining a good approximation to the real system. Additionally, the charged nature of most of the analyzed species forced us to include solvent effects in the estimation of energies in order to better reproduce the experimental conditions (see Computational Details).

The acceptability of excluding the cation in all calculations was demonstrated by comparing the structures of “naked” and potassium enolates (**2'** and **2'·K**, respectively). In accordance with the well-known weakly coordinating character of potassium, the geometries displayed in Figure 3 both with and without the cation are very similar, and therefore the absence of potassium, which in turn simplifies the calculations, is justified.

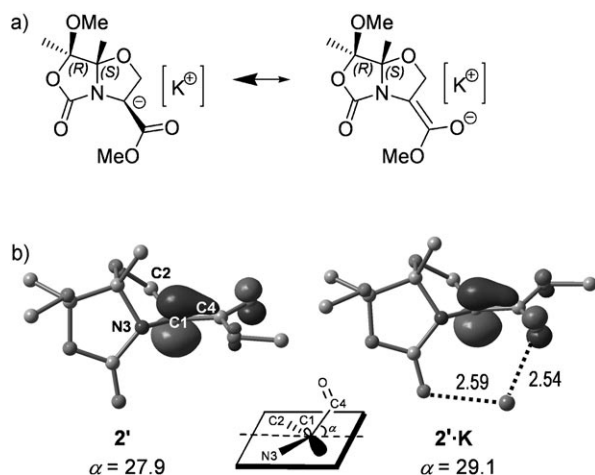


Figure 3. a) Structure of enolate **2'** showing the greater contribution of the carbanionic resonance form. b) Minimum-energy structures and HOMO of “naked” (**2'**) and potassium (**2'·K**) enolates, calculated at the B3LYP/6-31+G(d) level of theory. Distances are given in Å and angle  $\alpha$  in degrees.

A key feature found in these preliminary studies was the abnormally pronounced nonplanar character of both the “naked” and potassium enolates. Seebach et al.<sup>[12]</sup> measured this deviation from planarity (pyramidalization) in terms of the out-of-plane angle  $\alpha$  between the C1–C4 bond vector and the C1–C2–N3 plane, which ranges from 0° in a pure  $sp^2$  center to 54.7° in a typical  $sp^3$  center. Thus, the large calculated values of  $\alpha$  (ca. 29°), together with the non-symmetric character (different shape and size of each lobe) of the HOMO along the C1–C4 bond (Figure 3), provide the first

strong evidence pointing to retention of configuration of the stereocenter after deprotonation. This phenomenon is seen to a greater extent among other carbanionic species,<sup>[13]</sup> but very little theoretical evidence for pyramidalized enolates has been reported to date.<sup>[14]</sup> Moreover, to the best of our knowledge, all reported calculations concerning the stereoselective alkylation of enolates refer to cyclic or bicyclic lactams (diazepine-2-ones,<sup>[15]</sup> pyrrolidinones,<sup>[16]</sup> oxazolopiperidones<sup>[17]</sup>) or lactones,<sup>[18]</sup> in which the enolate moiety is endocyclic; in our case the enolate is exocyclic.

This theoretically found pyramidalization is supported by previous X-ray crystal structures of two imidazolidinone-derived silyl enol ethers.<sup>[12]</sup> These cyclic pyramidalized structures observed in the solid state retain the configuration of the starting imidazolidinones, which could be correlated with the high stereoselectivity achieved in the alkylation reactions.<sup>[12]</sup>

Unfortunately, the existence of the aforementioned competitive retro-*O*-Michael reaction, even at very short reaction times, made it impossible to experimentally measure the stereoselectivity of enolate protonation, at least in an acceptable way. This could have been a powerful tool to evaluate the energy barrier of pyramidal inversion.

It was possible, however, to isolate a small amount of starting bicycle **2** when the retro-*O*-Michael reaction was not fully complete (1 min). The properties of this compound (NMR, optical activity) were found to be identical to those previously measured prior to the reaction. Moreover, on quenching this test reaction with saturated [ $D_4$ ]ammonium chloride, the  $\alpha$ -deuterated analogue of **2** could be isolated as a single diastereomer (d.r. > 20:1)<sup>[5]</sup> with the same starting configuration at all stereocenters, as demonstrated by NMR spectroscopy in an analogous manner to **2**. These experimental probes demonstrated the retention of chirality during the deprotonation/protonation (deuteration) process.

With these findings in hand, it was reasonable to believe that the highly pyramidalized enolate must invert before being alkylated on the other face. We therefore investigated pyramidal inversion as a competitive pathway which could be the true source of the high degree of stereodifferentiation observed. All of the reaction profiles calculated from enolate **2'** are shown in Figure 4 and the energy barriers and intermediates (only the minimum-energy conformers) are summarized in Table 2.

As can be seen from Table 2, the inclusion of solvation dramatically alters the distribution of relative energies and makes some reaction channels more accessible in solution. The reacting species whose negative charge is partially or completely cancelled (i.e., in alkylation processes) are poorly solvated compared to those whose negative charge remains unaltered (i.e., in enolate inversion and retro-*O*-Michael reactions). As a consequence, diastereoselective *C*-alkylation (the exclusive reaction in the gas phase) and retro-*O*-Michael reaction become competitive pathways in solution, and this leads to a 94:5 ratio of products **5a** and **6** based on the Boltzmann distribution obtained from Gibbs free energies of each TS under Curtin–Hammett conditions.

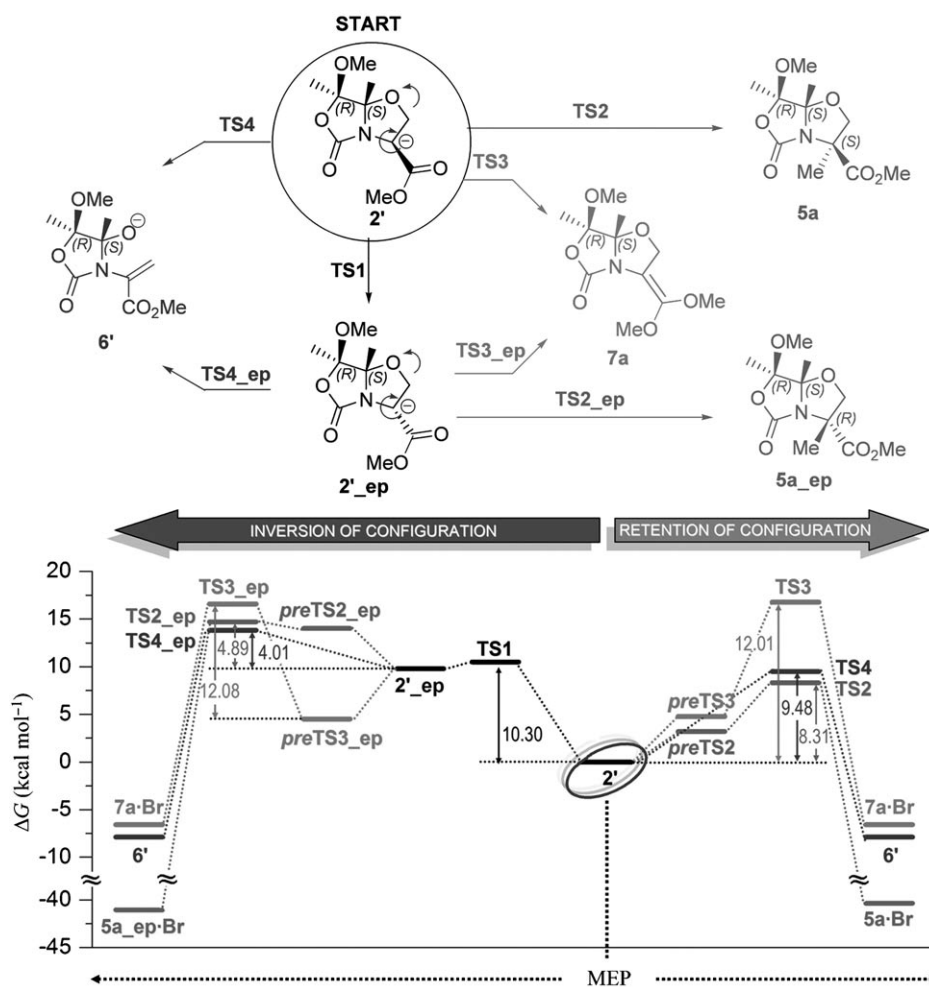


Figure 4. Reaction channels including minimum-energy paths (MEP) explored in the computational study starting from enolate **2'**: pyramidal inversion, C-alkylation, O-alkylation and retro-O-Michael reaction.

Table 2. Calculated [B3LYP/6-31+G(d)] activation barriers and relative energies<sup>[a]</sup> [kcal mol<sup>-1</sup>] of the intermediates and transition structures (TS).<sup>[b]</sup>

Structure	Gas phase ( $\epsilon=1.00$ )		THF ( $\epsilon=7.58$ )		
	$\Delta E_0$	$\Delta G$	$\Delta\Delta G_{\text{solv}}^{\text{[c]}}$	$\Delta E_0$	$\Delta G$
<b>2'</b>	0.00	0.00	0.00	0.00	0.00
<b>TS1</b>	12.58	13.04	-2.74	9.84	10.30
<b>2'_ep</b>	10.71	10.97	-1.17	9.54	9.80
<b>preTS2</b>	-13.08	-7.13	10.33	-2.75	3.20
<b>TS2</b>	-5.42	1.52	6.79	1.37	8.31
<b>5a-Br</b>	-49.20	-41.93	1.56	-47.64	-40.37
<b>preTS2_ep</b>	-2.69	3.53	10.47	7.78	14.00
<b>TS2_ep</b>	0.35	7.30	7.39	7.74	14.69
<b>5a_ep-Br</b>	-49.06	-41.72	0.67	-48.39	-41.05
<b>preTS3</b>	-10.45	-5.56	10.33	-0.12	4.77
<b>TS3</b>	4.39	10.63	6.15	10.54	16.78
<b>preTS3_ep</b>	-10.23	-4.85	9.34	-0.89	4.49
<b>TS3_ep</b>	3.81	10.15	6.42	10.23	16.57
<b>7a-Br</b>	-15.56	-8.29	1.70	-13.86	-6.59
<b>TS4</b>	6.84	6.73	2.75	9.59	9.48
<b>TS4_ep</b>	13.24	13.81	0.00	13.24	13.81
<b>6'</b>	-9.10	-9.43	1.55	-7.55	-7.88

[a]  $\Delta E_0$  values include zero-point energy (ZPE) corrections at the same level of theory. [b] The initial enolate and methyl bromide were arbitrarily chosen as the zero level in the relative-energy calculations. [c] Calculated at the IEF-PCM/B3LYP/6-31+G(d) level.

The greater stability of **2'** with respect to **2'\_ep** (by 9.8 kcal mol<sup>-1</sup>) is mainly caused by the strong stereoelectronic repulsions between the N3 lone pair and the  $\pi$  bond between C1 and C4 in **2'\_ep**, where the most important charge contribution is located at the  $p_z$  orbital of C1. This atom bears most of the negative charge of that bond and consequently repels the N3 lone pair, as we confirmed through NBO calculations (see Computational Details and Supporting Information). More interestingly, the barrier for pyramidal inversion of enolate **2'** (**TS1**) is about 2 kcal mol<sup>-1</sup> higher in energy than **TS2** (leading to less than 1% of epimer **2'\_ep**), a situation that implies complete retention of chirality in the C-alkylation of this substrate. Moreover, once the enolate has inverted, it must overcome a second activation barrier to complete the disfavored C-alkylation, which represents an overall barrier of about 15 kcal mol<sup>-1</sup>. Applying the equations of the Eyring transition-state theory to the calculated energy barriers, we could estimate half-lives ( $t_{1/2}$ )

of 59.2 and 0.3 ms for enolate **2'** in inversion and C-alkylation processes at -78 °C, respectively. These results are in very good agreement with the experimental observations discussed before.

The geometries of the minimum energy transition structures (TS) for each process are shown in Figure 5 (see Supporting Information for complete characterization of all conformers located for each stationary point, including pre- and post-transition structures). The pyramidalization of C1 in all species, as revealed by their  $\alpha$  values, is noteworthy.

Interestingly, **TS1** maintains some pyramidalization away from the ideal planar transition structure due to its late character, which makes it very similar in geometry and energy (by less than 1 kcal mol<sup>-1</sup> in solution) to **2'\_ep**. The even more pyramidal character of **2'\_ep** with respect to **2'** (ca. 8°) is related to the lower energy barrier calculated from **2'\_ep** to **TS2\_ep** (4.89 kcal mol<sup>-1</sup> in solution) with respect to that from **2'** to **TS2** (8.31 kcal mol<sup>-1</sup> in solution), in accordance with Hammond's postulate.

The HOMO in **TS1** has a more symmetrical character than those in **2'** and **2'\_ep**. The pyramidal inversion from

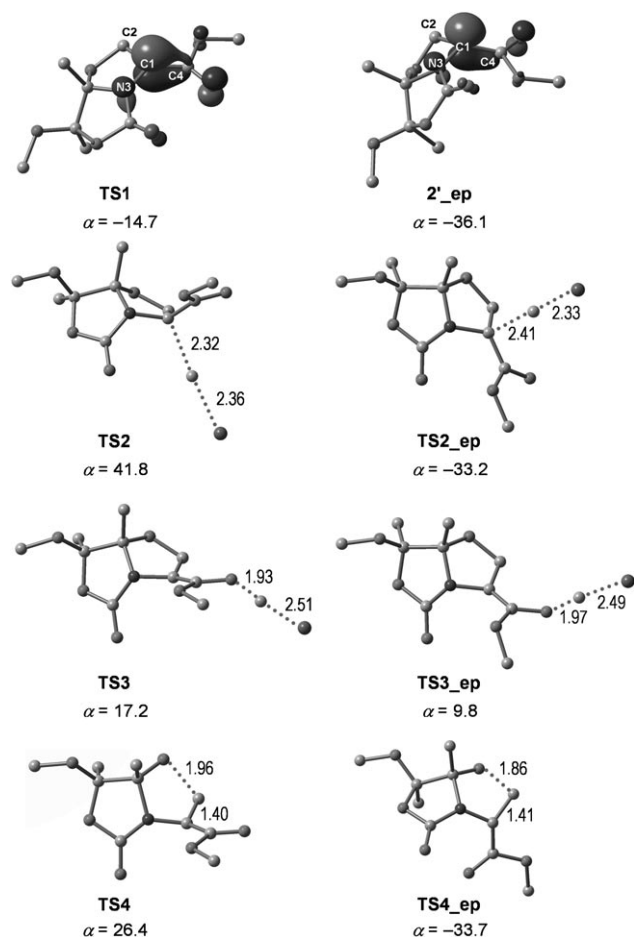


Figure 5. Minimum-energy transition structures for all reaction pathways evaluated from enolate 2' including intermediate 2'\_ep, calculated at the B3LYP/6-31+G(d) level of theory. Distances are given in Å and angles  $\alpha$  in degrees. HOMOs are displayed for TS1 and 2'\_ep.

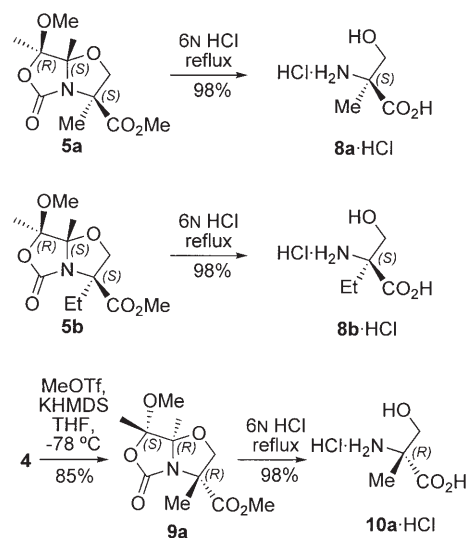
enolate 2' to 2'\_ep is rather complex and is associated with a conformational change at the oxazolidine ring. This is the reason why IRC calculations failed when following the reaction coordinate to the most stable enolate 2', even when using a broad range of step sizes (0.1–1.0 amu<sup>1/2</sup> Bohr). For the remainder of the structures, this lack of planarity is more noticeable in C-alkylation and, to a lesser extent, in the retro-*O*-Michael TS. However, *O*-alkylation TS have a more planar character (moreover, C1 has inverted in TS3\_ep), as expected on account of the delocalization of electronic density along the incipient ketene acetalic system.

In summary, the stereoselectivities achieved with these substrates along with the theoretical study in this work represent another case of the proposal enunciated by Seebach,<sup>[12]</sup> in which the stereoselectivity of a reaction can be correlated with pyramidalization.

**Synthesis of quaternary  $\alpha$ -alkyl  $\alpha$ -amino acids:** Given the results on the asymmetric alkylation of chiral building block 2, we decided to extend this methodology to the synthesis of some quaternary  $\alpha$ -alkyl  $\alpha$ -amino acids.<sup>[20]</sup> To achieve this

goal, and as a representative example, we transformed 5a and 5b into the corresponding (*S*)- $\alpha$ -methylserine (8a) and (*S*)- $\alpha$ -ethylserine (8b).

This was achieved by simple acid hydrolysis with 6N aqueous HCl under reflux (Scheme 4). The experimental data



Scheme 4. Synthesis of  $\alpha$ -alkyl serines 8a, 8b, and 10a.

obtained for these compounds agree with those previously reported in the literature.<sup>[1d,19]</sup> Considering the importance and the extended use of non-natural  $\alpha$ -methylated  $\alpha$ -amino acids,<sup>[20]</sup> especially (*S*)- $\alpha$ -methylserine (8a) as an inducer of  $\alpha$ -helix conformations when incorporated into peptides,<sup>[21]</sup> and the small number of suitable methods to obtain them on a large scale,<sup>[1d,22]</sup> we also present here a new synthetic strategy to obtain the *R* isomer. Thus, alkylation of chiral building block 4 with methyl triflate followed by acid hydrolysis gave (*R*)- $\alpha$ -methylserine (10a) in good yield in three steps from *N*-Boc-D-serine methyl ester 3 (Scheme 4).

## Conclusion

In summary, a short and general strategy for the multigram-scale preparation of chiral serine-derived building blocks has been developed. We first investigated their outstanding diastereoselective alkylation, which occurs with efficient retention of configuration. The mechanism involved in this alkylation process has been studied from a theoretical point of view, with inclusion of solvation effects, and the retention of the configuration at the defined stereocenter derives from the high degree of pyramidalization of the ester enolate. As a synthetic application, we also synthesized a variety of enantiomerically pure quaternary  $\alpha$ -alkyl  $\alpha$ -amino acids with the serine skeleton. The extensive use of these chiral serine-derived building blocks as important starting materials in stereocontrolled organic synthesis will continue to be explored in the future.

## Experimental Section

**General procedures:** Solvents were purified according to standard procedures. Analytical TLC was performed on Polychrom SI F254 plates. Column chromatography was performed with silica gel 60 (230–400 mesh).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on Bruker ARX 300 and Bruker Avance 400 spectrometers.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  with TMS as internal standard and in  $\text{D}_2\text{O}$  with TMS as external standard in a coaxial microtube. Melting points were determined on a Büchi B-545 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. Microanalyses were carried out on a CE Instruments EA-1110 analyser and are in good agreement with the calculated values.

**(3S,7R,7aS)-Tetrahydro-7-methoxy-7,7a-dimethyl-5-oxo-2H-oxazolo[3,2-c]oxazole-3-carboxylic acid methyl ester (2):** Method A: Triphenylphosphine hydrobromide (20.3 mg, 0.06 mmol) was added to a solution of (*S*)-*N*-Boc-serine methyl ester (100 mg, 0.46 mmol) and 2,3-dimethoxy-1,3-butadiene (63 mg, 0.55 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (5 mL) at room temperature. After stirring for 24 h, the mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (10 mL). The organic phase was washed with saturated  $\text{NaHCO}_3$  and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate 8/2) to give **2** as a yellow oil (12.8 mg, 0.05 mmol, 11% yield). Method B: A round-bottomed flask was charged with (*S*)-*N*-Boc-serine methyl ester (11.18 g, 45.58 mmol), 2,2,3,3-tetramethoxybutane (16.26 g, 91.19 mmol), toluene (300 mL) and  $\text{TsOH}\cdot\text{H}_2\text{O}$  (0.86 g, 4.57 mmol). The solution was heated under reflux and stirred for 3 h. The reaction mixture was cooled to room temperature, diluted with diethyl ether (100 mL) and then quenched with saturated  $\text{NaHCO}_3$  (100 mL). The aqueous phase was extracted with diethyl ether (2 × 80 mL). The organic layers were combined, washed with brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated and the crude product purified by column chromatography (hexane/ethyl acetate 9/1) to give **2** as a yellow oil (9.37 g, 31.91 mmol, 75% yield).  $[\alpha]_{\text{D}}^{25} = -118.1$  ( $c = 1.20$  in  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 4.77$  (dd,  $J = 5.9$  Hz,  $J = 9.0$  Hz, 1H; CH), 4.30 (t,  $J = 8.9$  Hz, 1H;  $\text{CH}_2$ ), 4.15 (dd,  $J = 5.9$  Hz,  $J = 8.8$  Hz, 1H;  $\text{CH}_2$ ), 3.82 (s, 3H;  $\text{CO}_2\text{CH}_3$ ), 3.47 (s, 3H;  $\text{OCH}_3$ ), 1.58 (s, 3H;  $\text{CH}_3$ ), 1.36 ppm (s, 3H;  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.5$  ( $\text{CO}_2\text{CH}_3$ ), 160.6 ( $\text{NCO}_2$ ), 107.1 ( $\text{CCH}_3\text{OCH}_3$ ), 101.5 ( $\text{CNCH}_3\text{OCH}_2$ ), 66.7 ( $\text{CH}_2$ ), 59.9 (CH), 52.9 ( $\text{CO}_2\text{CH}_3$ ), 51.0 ( $\text{OCH}_3$ ), 16.2 ( $\text{CH}_3$ ), 15.5 ppm ( $\text{CH}_3$ ); MS ( $\text{ESI}^+$ ):  $m/z$ : 246.1; elemental analysis calcd (%) for  $\text{C}_{10}\text{H}_{15}\text{NO}_6$ : C 48.98, H 6.17, N 5.71; found: C 48.88, H 6.22, N 5.68.

**(3R,7S,7aR)-Tetrahydro-7-methoxy-7,7a-dimethyl-5-oxo-2H-oxazolo[3,2-c]oxazole-3-carboxylic acid methyl ester (4):** As described for its enantiomer **2**, compound **4** (1.73 g, 7.03 mmol) was obtained by the same methodology, but by using (*R*)-*N*-Boc-serine methyl ester (2.06 g, 9.39 mmol) as starting material; yield: 75%.  $[\alpha]_{\text{D}}^{25} = +120.2$  ( $c = 1.27$  in  $\text{CHCl}_3$ ). The spectroscopic data are identical to those described for its enantiomer. Elemental analysis calcd (%) for  $\text{C}_{10}\text{H}_{15}\text{NO}_6$ : C 48.98, H 6.17, N 5.71; found: C 48.91, H 6.15, N 5.69.

**General procedure for alkylation reactions:** Compound **2** or **4** (0.90 mmol) was dissolved in dry THF (15 mL) under argon atmosphere and, if necessary, HMPA (3.60 mmol) was added with a syringe, and then the solution was stirred at  $-78^\circ\text{C}$ . Alkylating agent (2.70 mmol) and a 0.91 M solution of KHMDs in THF (1.35 mmol) were added with a syringe (KHMDs was added slowly). After the reaction mixture was stirred for 5 min, the reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  solution (15 mL). This mixture was warmed to room temperature and vigorously stirred. The crude product was diluted with diethyl ether and the aqueous phase was separated and extracted again with more diethyl ether. The organic layers were combined, washed with brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated, and the crude purified by column chromatography on silica gel to give **5a–d** (from **2**) or **9a** (from **4**).

**(3S,7R,7aS)-Tetrahydro-7-methoxy-3,7,7a-trimethyl-5-oxo-2H-oxazolo[3,2-c]oxazole-3-carboxylic acid methyl ester (5a):** Compound **5a** (1.81 g, 6.96 mmol) was obtained from compound **2** (2 g, 8.20 mmol), after purification (hexane/ethyl acetate 1/1), as a colourless oil; yield: 85%.  $[\alpha]_{\text{D}}^{25} = -95.4$  ( $c = 1.05$  in  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 4.59$  (d,  $J =$

8.8 Hz, 1H;  $\text{CH}_2$ ), 3.87 (d,  $J = 8.8$  Hz, 1H;  $\text{CH}_2$ ), 3.81 (s, 3H;  $\text{CO}_2\text{CH}_3$ ), 3.46 (s, 3H;  $\text{OCH}_3$ ), 1.81 (s, 3H;  $\text{CH}_3$ ), 1.54 (s, 3H;  $\text{CH}_3$ ), 1.34 ppm (s, 3H;  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 173.2$  ( $\text{CO}_2\text{CH}_3$ ), 155.0 ( $\text{NCO}_2$ ), 106.8 ( $\text{CCH}_3\text{OCH}_3$ ), 102.6 ( $\text{CNCH}_3\text{OCH}_2$ ), 76.5 ( $\text{CH}_2$ ), 66.2 ( $\text{CCO}_2\text{CH}_3$ ), 53.0 ( $\text{CO}_2\text{CH}_3$ ), 51.3 ( $\text{OCH}_3$ ), 20.5 ( $\text{CH}_3$ ), 17.8 ( $\text{CH}_3$ ), 16.3 ppm ( $\text{CH}_3$ ); MS ( $\text{ESI}^+$ ):  $m/z$ : 260.1; elemental analysis calcd (%) for  $\text{C}_{11}\text{H}_{17}\text{NO}_6$ : C 50.96, H 6.61, N 5.40; found: C 50.66, H 6.70, N 5.38.

**(3S,7R,7aS)-Tetrahydro-3-ethyl-7-methoxy-7,7a-dimethyl-5-oxo-2H-oxazolo[3,2-c]oxazole-3-carboxylic acid methyl ester (5b):** Compound **5b** (64 mg, 0.24 mmol) was obtained from compound **2** (46 mg, 0.17 mmol), after purification (hexane/ethyl acetate 1/1), as a colorless solid; yield: 70%. m.p.  $71\text{--}73^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{25} = -39.1$  ( $c = 1.02$  in  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 4.64$  (d,  $J = 8.9$  Hz, 1H;  $\text{CH}_2$ ), 3.91 (d,  $J = 8.9$  Hz, 1H;  $\text{CH}_2$ ), 3.81 (s, 3H;  $\text{CO}_2\text{CH}_3$ ), 3.45 (s, 3H;  $\text{OCH}_3$ ), 2.44–2.53 (m, 1H;  $\text{CH}_2\text{CH}_3$ ), 2.05–2.14 (m, 1H;  $\text{CH}_2\text{CH}_3$ ), 1.54 (s, 3H;  $\text{CH}_3$ ), 1.32 (s, 3H;  $\text{CH}_3$ ), 0.95 ppm (t,  $J = 7.4$ , 3H;  $\text{CH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 172.5$  ( $\text{CO}_2\text{CH}_3$ ), 154.6 ( $\text{NCO}_2$ ), 106.7 ( $\text{CCH}_3\text{OCH}_3$ ), 102.4 ( $\text{CNCH}_3\text{OCH}_2$ ), 73.9 ( $\text{CH}_2$ ), 70.0 ( $\text{CCO}_2\text{CH}_3$ ), 52.8 ( $\text{CO}_2\text{CH}_3$ ), 51.2 ( $\text{OCH}_3$ ), 26.0 ( $\text{CH}_2\text{CH}_3$ ), 18.1 ( $\text{CH}_3$ ), 16.5 ( $\text{CH}_3$ ), 9.2 ppm ( $\text{CH}_2\text{CH}_3$ ); MS ( $\text{ESI}^+$ ):  $m/z$ : 274.1; elemental analysis calcd (%) for  $\text{C}_{12}\text{H}_{19}\text{NO}_6$ : C 52.74, H 7.01, N 5.13; found: C 52.70, H 7.03, N 5.13.

**(3S,7R,7aS)-Tetrahydro-3-benzyl-7-methoxy-7,7a-dimethyl-5-oxo-2H-oxazolo[3,2-c]oxazole-3-carboxylic acid methyl ester (5c):** Compound **5c** (80 mg, 0.24 mmol) was obtained from **2** (196 mg, 0.80 mmol), after purification (hexane/ethyl acetate 8/2), as a white solid; yield: 30%. m.p.  $111\text{--}113^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{25} = -117.4$  ( $c = 1.09$  in  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.32\text{--}7.10$  (m, 5H; Ph), 4.56 (d,  $J = 9.1$  Hz, 1H;  $\text{CH}_2$ ), 4.18 (d,  $J = 9.1$  Hz, 1H;  $\text{CH}_2$ ), 4.00 (d,  $J = 13.8$  Hz, 1H;  $\text{CH}_2\text{Ph}$ ), 3.74 (s, 3H;  $\text{CO}_2\text{CH}_3$ ), 3.45 (s, 3H;  $\text{OCH}_3$ ), 3.23 (d,  $J = 13.8$  Hz, 1H;  $\text{CH}_2\text{Ph}$ ), 1.41 (s, 3H;  $\text{CH}_3$ ), 1.32 ppm (s, 3H;  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 171.4$  ( $\text{CO}_2\text{CH}_3$ ), 154.6 ( $\text{NCO}_2$ ), 134.4, 130.0, 128.7, 127.6 (Ph), 107.3 ( $\text{CCH}_3\text{OCH}_3$ ), 102.2 ( $\text{CNCH}_3\text{OCH}_2$ ), 73.5 ( $\text{CH}_2$ ), 69.6 ( $\text{CCO}_2\text{CH}_3$ ), 52.9 ( $\text{CO}_2\text{CH}_3$ ), 51.5 ( $\text{OCH}_3$ ), 38.2 ( $\text{CH}_2\text{Ph}$ ), 18.5 ( $\text{CH}_3$ ), 16.4 ppm ( $\text{CH}_3$ ); MS ( $\text{ESI}^+$ ):  $m/z$ : 336.1; elemental analysis calcd (%) for  $\text{C}_{17}\text{H}_{21}\text{NO}_6$ : C 60.89, H 6.31, N 4.18; found: C 60.81, H 6.32, N 4.21.

**(3S,7R,7aS)-Tetrahydro-3-allyl-7-methoxy-7,7a-dimethyl-5-oxo-2H-oxazolo[3,2-c]oxazole-3-carboxylic acid methyl ester (5d):** Compound **5d** (28 mg, 0.10 mmol) was obtained from compound **2** (35 mg, 0.14 mmol), after purification (hexane/ethyl acetate 8/2), as a white solid; yield: 70%. m.p.  $47\text{--}49^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{25} = -74.5$  ( $c = 1.04$  in  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 5.82\text{--}5.64$  (m, 1H;  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.15–5.24 (m, 2H;  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 4.58 (d,  $J = 9.1$  Hz, 1H;  $\text{CH}_2$ ), 4.04 (d,  $J = 9.1$  Hz, 1H;  $\text{CH}_2$ ), 3.79 (s, 3H;  $\text{CO}_2\text{CH}_3$ ), 3.45 (s, 3H;  $\text{OCH}_3$ ), 3.12 (dd,  $J = 14.1$  Hz,  $J = 6.6$  Hz, 1H;  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 2.86 (dd,  $J = 14.1$  Hz,  $J = 7.8$  Hz, 1H;  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 1.53 (s, 3H;  $\text{CH}_3$ ), 1.33 ppm (s, 3H;  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 172.1$  ( $\text{CO}_2\text{CH}_3$ ), 154.6 ( $\text{NCO}_2$ ), 131.2 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 120.9 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 107.1 ( $\text{CCH}_3\text{OCH}_3$ ), 102.5 ( $\text{CNCH}_3\text{OCH}_2$ ), 73.9 ( $\text{CH}_2$ ), 68.6 ( $\text{CCO}_2\text{CH}_3$ ), 53.1 ( $\text{CO}_2\text{CH}_3$ ), 51.5 ( $\text{OCH}_3$ ), 37.3 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 18.0 ( $\text{CH}_3$ ), 16.7 ppm ( $\text{CH}_3$ ); MS ( $\text{ESI}^+$ ):  $m/z$ : 286.1; elemental analysis calcd (%) for  $\text{C}_{13}\text{H}_{19}\text{NO}_6$ : C 54.73, H 6.71, N 4.91; found: C 54.82, H 6.68, N 4.89.

**(4S,5R)-2-(4-Hydroxy-5-methoxy-4,5-dimethylloxazolidin-2-one-3-yl)-acrylic acid methyl ester (6):** Compound **2** (28 mg, 0.11 mmol) was dissolved in dry THF (5 mL) under argon atmosphere. The solution was cooled to  $-78^\circ\text{C}$  and stirred. A 0.91 M solution of KHMDs in THF (0.18 mL, 0.17 mmol) was added slowly with a syringe. After 10 min, the reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  solution (5 mL). The mixture was heated to room temperature in a warm water bath and vigorously stirred. The crude product was diluted with diethyl ether and the aqueous phase was extracted with more diethyl ether. The organic layers were combined, washed with brine, and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate 6/4) to give compound **6** as a colourless oil (26 mg, 0.10 mmol); yield: 95%.  $[\alpha]_{\text{D}}^{25} = -122.7$  ( $c = 1.10$  in  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.57$  (s, 1H;  $\text{C}=\text{CH}_2$ ), 5.99 (s, 1H;  $\text{C}=\text{CH}_2$ ), 4.71 (s, 1H; OH), 3.87 (s, 3H;  $\text{CO}_2\text{CH}_3$ ), 3.44 (s, 3H;  $\text{OCH}_3$ ), 1.62 (s, 3H;  $\text{CH}_3$ ), 1.36 ppm (s, 3H;  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 166.1$  ( $\text{CO}_2\text{CH}_3$ ), 154.9 ( $\text{NCO}_2$ ), 131.8 ( $\text{C}=\text{CH}_2$ ),

129.1 (C=CH<sub>2</sub>), 108.7 (CCH<sub>2</sub>OCH<sub>3</sub>), 90.8 (CNCH<sub>2</sub>OH), 53.2 (CO<sub>2</sub>CH<sub>3</sub>), 50.7 (OCH<sub>3</sub>), 19.6 (CH<sub>3</sub>), 14.6 ppm (CH<sub>3</sub>); MS (ESI<sup>+</sup>): *m/z*: 246.1; elemental analysis calcd (%) for C<sub>10</sub>H<sub>15</sub>NO<sub>6</sub>: C 48.98, H 6.17, N 5.71; found: C 49.03, H 6.15, N 5.77.

**(S)- $\alpha$ -Methylserine (8a):** A round-bottomed flask was charged with compound **5a** (221 mg, 0.85 mmol) and aqueous 6N HCl solution (10 mL). The mixture was stirred overnight under reflux. The solvent was removed in vacuo, and the residue was partitioned between water and ethyl acetate. The aqueous phase was evaporated to give the hydrochloride derivative of compound **8a** (130 mg, 98%). An aliquot of this material (72 mg) was treated with ethanol/propylene oxide (1/1, 2 mL) under reflux for 2 h to give compound **8a** (23 mg, 0.20 mmol) as a white solid; yield 41%. [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +5.3 (*c* = 1.16 in H<sub>2</sub>O). The spectroscopic data were identical to those reported in the literature.<sup>[14]</sup> MS (ESI<sup>+</sup>): *m/z*: 120.0; elemental analysis calcd (%) for C<sub>4</sub>H<sub>9</sub>NO<sub>3</sub>: C 40.33, H 7.62, N 11.76; found: C 40.24, H 7.63, N 11.72.

**(S)- $\alpha$ -Ethylserine (8b):** Starting from compound **5b** (64 mg, 0.24 mmol) and following the protocol described above for **8a**, compound **8b** (41 mg, 98%) was obtained as its hydrochloride derivative. The spectroscopic data were identical to those reported in the literature.<sup>[19b,c]</sup> An analytical sample of this (S)- $\alpha$ -ethylserine hydrochloride (20 mg) was treated with ethanol/propylene oxide (1/1, 2 mL) under reflux to give compound **8b** (9.5 mg, 0.07 mmol) as a white solid; yield 60%. [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -1.5 (*c* = 0.95 in H<sub>2</sub>O). <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O):  $\delta$  = 3.94 (d, *J* = 11.9 Hz, 1H; CH<sub>2</sub>), 3.68 (d, *J* = 11.9 Hz, 1H; CH<sub>2</sub>), 1.62–1.94 (m, 2H; CH<sub>2</sub>CH<sub>3</sub>), 0.94 ppm (dd, *J* = 10.1 Hz, *J* = 5.0 Hz, 3H; CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (75 MHz, D<sub>2</sub>O):  $\delta$  = 177.6 (CO<sub>2</sub>H), 69.6 (CCH<sub>2</sub>OH), 67.2 (CCH<sub>2</sub>OH), 28.4 (CH<sub>2</sub>CH<sub>3</sub>), 10.0 ppm (CH<sub>2</sub>CH<sub>3</sub>); MS (ESI<sup>+</sup>): *m/z*: 134.1; elemental analysis calcd (%) for C<sub>5</sub>H<sub>11</sub>NO<sub>3</sub>: C 45.10, H 8.33, N 10.52; found: C 45.20, H 8.30, N 10.46.

**(3R,7S,7aR)-Tetrahydro-7-methoxy-3,7,7a-trimethyl-5-oxo-2H-oxazolo-[3,2-c]oxazole-3-carboxylic acid methyl ester (9a):** As described for its enantiomer **5a**, compound **9a** (204 mg, 0.78 mmol) was obtained from compound **4** (200 mg, 0.82 mmol); yield: 95%. [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +92.1 (*c* = 1.05 in CHCl<sub>3</sub>). The spectroscopic data were identical to those described for its enantiomer; elemental analysis calcd (%) for C<sub>11</sub>H<sub>17</sub>NO<sub>6</sub>: C 50.96, H 6.61, N 5.40; found: C 50.95, H 6.70, N 5.42.

**(R)- $\alpha$ -Methylserine (10a):** As described for its enantiomer **8a**, the hydrochloride derivative of compound **10a** (109 mg, 98%) was obtained from compound **9a** (212 mg, 0.82 mmol). Similarly, an analytical sample (53 mg) was treated with ethanol/propylene oxide (1/1, 2 mL) under reflux to give compound **10a** (29 mg, 0.24 mmol) as a white solid; yield 70%. [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -6.3 (*c* = 0.98 in H<sub>2</sub>O). The spectroscopic data were identical to those described for its enantiomer; elemental analysis calcd (%) for C<sub>4</sub>H<sub>9</sub>NO<sub>3</sub>: C 40.33, H 7.62, N 11.76; found: C 40.24, H 7.63, N 11.72.

**2D NMR experiments:** NMR experiments were carried out on a Bruker Avance 400 spectrometer at 298 K. Magnitude-mode ge-2D COSY spectra were recorded with gradients by using the cosygpcqf pulse program with 90° pulse width. Phase-sensitive ge-2D HSQC spectra were recorded with a z-filter and selection before t1 with removal of the decoupling during acquisition by using the invgpnrdp pulse program with CNST2 (JHC) = 145. 2D NOESY experiments were carried out by using phase-sensitive ge-2D NOESY for spectra recorded in CDCl<sub>3</sub>.

**Computational details:** All calculations were carried out with the B3LYP hybrid functional<sup>[23]</sup> and 6-31+G(d) basis set. Full geometry optimizations and transition structure (TS) searches were carried out with the Gaussian03 package.<sup>[24]</sup> The possibility of different conformations was taken into account for all structures. BSSE corrections were not considered in this work. Frequency analyses were carried out at the same level used in the geometry optimizations, and the nature of the stationary points was determined in each case according to the appropriate number of negative eigenvalues of the Hessian matrix. Scaled frequencies were not considered since significant errors in the calculated thermodynamic properties are not found at this theoretical level.<sup>[25]</sup> Where necessary, mass-weighted intrinsic reaction coordinate (IRC) calculations were carried out by using the Gonzalez and Schlegel scheme<sup>[26]</sup> in order to ensure that the TSs indeed connected the appropriate reactants and products. Solvent effects were taken into account through the polarized continuum model (IEF-PCM)<sup>[27]</sup> using UAHF radii, as implemented in Gaussian03.

Depending on the individual case, the internally stored parameters for toluene and tetrahydrofuran were used to calculate solvation energies ( $\Delta G_{\text{soln}}$ ). Zero-point corrected ( $\Delta E_0$ ) and Gibbs free energies ( $\Delta G$ ) were used for the discussion on the relative stabilities of the considered structures. Second-order perturbation energies ( $E^{(2)}$ ),<sup>[28]</sup> as well as pairwise steric exchange energies for disjoint interactions ( $E^S$ ),<sup>[29]</sup> were calculated by natural bond orbital/natural localized molecular orbital (NBO/NLMO) analysis with the NBO 5.G program<sup>[30]</sup> and upgraded Gaussian03 as interface. These attractive and repulsive interactions were estimated by means of the localized  $\sigma$ ,  $\pi$ ,  $n$ ,  $\sigma^*$  and  $\pi^*$  valence orbitals.

Cartesian coordinates, electronic energies, entropies, enthalpies, Gibbs free energies, and lowest frequencies of the different conformations of all structures considered are available as Supporting Information.

**X-ray diffraction analysis:** Crystal data for **5b**: C<sub>12</sub>H<sub>19</sub>NO<sub>6</sub>, *M<sub>r</sub>* = 273.28, colourless prism, 0.5 × 0.3 × 0.2 mm, *T* = 173 K, orthorhombic, space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, *Z* = 4, *a* = 5.72920(10), *b* = 8.1401(2), *c* = 29.1363(8) Å, *V* = 1358.81(6) Å<sup>3</sup>,  $\rho_{\text{calcd}}$  = 1.336 g cm<sup>-3</sup>, *F*(000) = 584,  $\lambda$  = 0.71073 Å (MoK $\alpha$ ),  $\mu$  = 0.107 mm<sup>-1</sup>, Nonius kappa CCD diffractometer,  $\theta$  range 0.21–27.88°, 6939 collected reflections, 3156 unique reflections, full-matrix least-squares refinement (SHELXL97),<sup>[31]</sup> *R*<sub>1</sub> = 0.0373, *wR*<sub>2</sub> = 0.0895, [*R*<sub>1</sub> = 0.0523, *wR*<sub>2</sub> = 0.0970 (all data)], GOF = 1.036, residual electron density between 0.227 and -0.139 e Å<sup>-3</sup>. Hydrogen atoms were located from electron-density maps. Crystal data for **5d**: C<sub>13</sub>H<sub>19</sub>NO<sub>6</sub>, *M<sub>r</sub>* = 285.29, colourless prism, 0.4 × 0.2 × 0.1 mm, *T* = 173 K, orthorhombic, space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, *Z* = 4, *a* = 5.83440(10), *b* = 14.2883(2), *c* = 17.2023(3) Å, *V* = 1434.05(4) Å<sup>3</sup>,  $\rho_{\text{calcd}}$  = 1.322 g cm<sup>-3</sup>, *F*(000) = 608,  $\lambda$  = 0.71073 Å (MoK $\alpha$ ),  $\mu$  = 0.105 mm<sup>-1</sup>, Nonius kappa CCD diffractometer,  $\theta$  range 0.21–27.88°, 22960 collected reflections, 3420 unique reflections, full-matrix least-squares refinement (SHELXL97),<sup>[31]</sup> *R*<sub>1</sub> = 0.0395, *wR*<sub>2</sub> = 0.0930, [*R*<sub>1</sub> = 0.0529, *wR*<sub>2</sub> = 0.0991 (all data)], GOF = 1.069, residual electron density between 0.192 and -0.166 e Å<sup>-3</sup>. Hydrogen atoms were located by mixed methods (electron-density maps and theoretical positions).

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- [1] a) A. Avenoza, C. Cativiela, F. Corzana, J. M. Peregrina, M. M. Zurbano, *J. Org. Chem.* **1999**, *64*, 8220–8225; b) A. Avenoza, C. Cativiela, J. M. Peregrina, D. Sucunza, M. M. Zurbano, *Tetrahedron: Asymmetry* **1999**, *10*, 4653–4661; c) A. Avenoza, C. Cativiela, F. Corzana, J. M. Peregrina, M. M. Zurbano, *Tetrahedron: Asymmetry* **2000**, *11*, 2195–2204; d) A. Avenoza, C. Cativiela, F. Corzana, J. M. Peregrina, D. Sucunza, M. M. Zurbano, *Tetrahedron: Asymmetry* **2001**, *12*, 949–957; e) A. Avenoza, J. H. Busto, C. Cativiela, J. M. Peregrina, D. Sucunza, M. M. Zurbano, *Tetrahedron: Asymmetry* **2003**, *14*, 399–405; f) A. Avenoza, J. H. Busto, F. Corzana, J. M. Peregrina, D. Sucunza, M. M. Zurbano, *Tetrahedron: Asymmetry* **2004**, *15*, 719–724; g) A. Avenoza, J. H. Busto, F. Corzana, J. M. Peregrina, D. Sucunza, M. M. Zurbano, *Synthesis* **2005**, 575–578.
- [2] a) P. Garner, J. M. Park, *J. Org. Chem.* **1987**, *52*, 2361–2364; b) P. Garner, J. M. Park, *Org. Synth.* **1992**, *70*, 18–27; c) D. Seebach, J. D. Aebi, M. Gauder-Coquoz, R. Naef, *Helv. Chim. Acta* **1987**, *70*, 1194–1216; d) A. Avenoza, C. Cativiela, F. Corzana, J. M. Peregrina, M. M. Zurbano, *Synthesis* **1997**, 1146–1150; e) X. Liang, J. Andersch, M. Bols, *J. Chem. Soc. Perkin Trans. 1* **2001**, 2136–2157; f) D. J. Dixon, C. I. Harding, S. V. Ley, D. M. G. Tilbrook, *Chem. Commun.* **2003**, 468–469; g) M. Brunner, T. Straub, P. Saarenketo, K. Rissanen, A. M. P. Koskinen, *Lett. Org. Chem.* **2004**, *1*, 268–270; h) M. Brunner, A. M. P. Koskinen, *Tetrahedron Lett.* **2004**, *45*, 3063–3065; i) A. McKillop, R. J. K. Taylor, R. J. Watson, N. Lewis, *Synthe-*



- sis **1994**, 31–32; j) L. Williams, Z. Zhang, F. Shao, P. J. Carroll, M. M. Joullié, *Tetrahedron* **1996**, 52, 11673–11694.
- [3] a) S. V. Ley, E. Díez, D. J. Dixon, R. T. Guy, P. Michel, G. L. Natrass, T. D. Sheppard, *Org. Biomol. Chem.* **2004**, 2, 3608–3617; b) N. L. Douglas, S. V. Ley, H. M. L. Osborn, D. R. Owen, H. W. M. Priepeke, S. L. Warriner, *Synlett* **1996**, 793–795.
- [4] J.-L. Montchamp, F. Tian, M. E. Hart, J. W. Frost, *J. Org. Chem.* **1996**, 61, 3897–3899.
- [5] We have expressed the corresponding diastereomeric ratio as follows: d.r. >20:1, because a single stereoisomer of each of the final compounds was detected by <sup>1</sup>H NMR.
- [6] C. I. Harding, D. J. Dixon, S. V. Ley, *Tetrahedron* **2004**, 60, 7679–7692.
- [7] C. Agami, F. Couty, *Tetrahedron* **2002**, 58, 2701–2724.
- [8] M. Brunner, P. Saarenketo, T. Straub, K. Rissanen, A. M. P. Koskinen, *Eur. J. Org. Chem.* **2004**, 3879–3883.
- [9] CCDC-629276 (**5b**) and CCDC-629275 (**5d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- [10] D. Seebach, B. Lamatsch, R. Amstutz, A. K. Beck, M. Dobler, M. Egli, R. Fitz, M. Gautschi, B. Herradon, P. C. Hidber, J. J. Irwin, R. Locher, M. Maestro, T. Maetzke, A. Mourino, E. Pfammatter, D. A. Plattner, C. Schickli, W. B. Schweizer, P. Seiler, G. Stucky, W. Petter, J. Escalante, E. Juaristi, D. Quintana, C. Miravittles, E. Molins, *Helv. Chim. Acta* **1992**, 75, 913–934.
- [11] a) H. Park, J. Lee, M. J. Kang, Y.-J. Lee, B.-S. Jeong, J.-H. Lee, M.-S. Yoo, M.-J. Kim, S. Choi, S. Jew, *Tetrahedron* **2004**, 60, 4243–4249; b) P. J. Reider, R. S. Eichen, E. Conn, P. Davis, V. J. Granda, A. J. Zambito, E. J. J. Gravowski, *J. Org. Chem.* **1987**, 52, 3326–3334.
- [12] D. Seebach, T. Maetzke, W. Petter, B. Klötzer, D. A. Plattner, *J. Am. Chem. Soc.* **1991**, 113, 1781–1786.
- [13] a) E. Buncl, J. M. Dust, *Carbanion Chemistry: Structures and Mechanisms*, American Chemical Society, Washington, DC, **2003**; b) H.-U. Reissig, I. Bohm, *J. Am. Chem. Soc.* **1982**, 104, 1735–1737.
- [14] a) S. Hoz, C. Azran, A. Sella, *J. Am. Chem. Soc.* **1996**, 118, 5456–5461; b) Y. Ikuta, S. Tomoda, *Tetrahedron Lett.* **2003**, 44, 5931–5934.
- [15] a) H. Zhao, D. C. Hsu, P. R. Carlier, *Synthesis* **2005**, 1–16; b) P. R. Carlier, P. C.-H. Lam, J. C. DeGuzman, H. Zhao, *Tetrahedron: Asymmetry* **2005**, 16, 2998–3002.
- [16] K. Ando, N. S. Green, Y. Lee, K. N. Houk, *J. Am. Chem. Soc.* **1999**, 121, 5334–5335.
- [17] I. Soteras, O. Lozano, A. Gómez-Esqué, C. Escolano, M. Orozco, M. Amat, J. Bosch, F. J. Luque, *J. Am. Chem. Soc.* **2006**, 128, 6581–6588.
- [18] a) K. Ando, *J. Am. Chem. Soc.* **2005**, 127, 3964–3972; b) Y. Ikuta, S. Tomoda, *Org. Lett.* **2004**, 6, 189–192.
- [19] a) D. Seebach, J. D. Aebi, M. Gander-Coquoz, R. Naef, *Helv. Chim. Acta* **1987**, 70, 1194–1216; b) Y. Ito, M. Sawamura, E. Shirakawa, K. Hayashizaki, T. Hayashi, *Tetrahedron Lett.* **1988**, 29, 235–238; c) N. Takamura, S. Terashima, K. Arhiwa, S. Yamada, *Chem. Pharm. Bull.* **1967**, 15, 1776–1784.
- [20] a) S. Mzengeza, T. K. Venkatachalam, M. Diksic, *Amino Acids* **2000**, 18, 81–88; b) C. Catiuela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, 9, 3517–3599; c) Y. Ohfuné, T. Shinada, *Eur. J. Org. Chem.* **2005**, 5127–5143.
- [21] a) A. L. Morris, M. W. MacArthur, E. G. Hutchinson, J. M. Thornton, *Protein Struct. Funct. Genet.* **1992**, 12, 345–364; b) E. Altmann, K.-H. Altmann, K. Nebel, M. Mutter, *Int. J. Pept. Protein Res.* **1988**, 32, 344–349; c) V. Pavone, B. Di Blasio, A. Lombardi, O. Maglio, C. Isernia, C. Pedone, E. Benedetti, E. Altmann, M. Mutter, *Int. J. Pept. Protein Res.* **1993**, 41, 15–20; d) H. Mickos, K. Sundberg, B. Luning, *Acta Chem. Scand.* **1992**, 46, 989–993; e) D. Obrecht, M. Altorfer, C. Lehmann, P. Schönholzer, K. Müller, *J. Org. Chem.* **1996**, 61, 4080–4086.
- [22] a) N. D. Smith, M. Goodman, *Org. Lett.* **2003**, 5, 1035–1037; b) N. D. Smith, A. M. Wohlrab, M. Goodman, *Org. Lett.* **2005**, 7, 255–258.
- [23] a) C. Lee, W. Yang, R. Parr, *Phys. Rev. B* **1988**, 37, 785–789; b) A. D. Becke, *J. Chem. Phys.* **1993**, 98, 5648–5652.
- [24] Gaussian03, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.
- [25] C. W. Bauschlicher, Jr., *Chem. Phys. Lett.* **1995**, 246, 40–44.
- [26] a) C. Gonzalez, H. B. Schlegel, *J. Chem. Phys.* **1989**, 90, 2154–2161; b) C. Gonzalez, H. B. Schlegel, *J. Chem. Phys.* **1990**, 94, 5523–5527.
- [27] a) M. Cossi, V. Barone, B. Mennucci, J. Tomasi, *Chem. Phys. Lett.* **1998**, 286, 253–260; b) J. Tomasi, B. Mennucci, E. Cancès, *J. Mol. Struct.* **1999**, 464, 211–226; c) M. Cossi, G. Scalmani, N. Rega, V. Barone, *J. Chem. Phys.* **2002**, 117, 43–54, and references therein; d) J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, 105, 2999–3093.
- [28] a) A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, 88, 899–926; b) F. Weinhold, *Natural Bond Orbital Methods in Encyclopedia of Computational Chemistry, Vol. 3*, (Ed.: P. von R. Schleyer), **1998**, pp. 1792–1811.
- [29] a) J. K. Badenhop, F. Weinhold, *J. Chem. Phys.* **1997**, 107, 5406–5421; b) J. K. Badenhop, F. Weinhold, *J. Chem. Phys.* **1997**, 107, 5422–5432; c) J. K. Badenhop, F. Weinhold, *Int. J. Quantum Chem.* **1999**, 72, 269–280.
- [30] NBO 5.0, E. D. Glendening, J. K. Badenhop, A. E. Reed, J. E. Carpenter, J. A. Bohmann, C. M. Morales, F. Weinhold, Theoretical Chemistry Institute, University of Wisconsin, Madison, **2001**.
- [31] G. M. Sheldrick, SHELXL97, Program for the refinement of crystal structures, University of Göttingen, Germany, **1997**.

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