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A Domino Michael/Dieckmann Process as an Entry to α-(Hydroxymethyl)glutamic Acid

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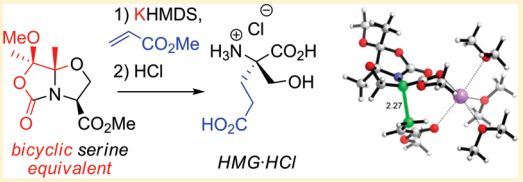
Supporting Information

ABSTRACT: A domino process that involves a Michael-type addition followed by a Dieckmann reaction mediated by the participation of the cyclic carbamate group is the key step in the synthesis of both enantiomers of α-(hydroxymethyl)glutamic acid (HMG).



INTRODUCTION

L-Glutamic acid (L-Glu) is the major excitatory amino acid neurotransmitter that acts on the central nervous system and is involved in many important neural processes such as learning, memory, brain development, and neurotoxicity.[1] Accordingly, glutamate receptors are considered as potential therapeutic targets. Two main types of receptors have been characterized: the ionotropic (iGluR) and metabotropic receptors (mGluR). In an attempt to study the roles of these latter receptors and their modulation mechanism in the nervous system, huge efforts have been devoted to the discovery of selective agonists and antagonists on mGluRs. Kozikowski et al. stated that (2*S*)-(hydroxymethyl)glutamic acid (*S*)-**1** (HMG) was a potent mGluR3 agonist and a weak mGluR2 antagonist.[2] Since this initial work, in which the authors envisioned a Michael addition of a serine-derived oxazolidine to methyl acrylate as the key step to obtain HMG and its γ-substituted analogues, a variety of synthetic methods for the construction of enantiopure HMG (*R*)-**1** and (*S*)-**1** and derivatives have been published.[2−8] Now, as part of our research project on α-alkylserine derivatives,[9] we report here an efficient synthesis of both enantiomers of HMG (Figure 1).

Recently, in the context of the synthesis of α-alkylserines, we have published a new methodology involving the use of a serine equivalent as an excellent chiral building block.[10] Indeed, starting from the bicyclic *N,O*-acetal **4**, a diastereoselective enolate alkylation reaction to give compound **3** and a subsequent acid hydrolysis allow the synthesis of the required α-alkyl-β-hydroxy-α-amino acids with one stereogenic center (α-alkylserine derivatives **2**). Note the easy access to this chiral serine-derived building block **4** (gram scale, one step)[10a] from commercially available *N*-Boc-L-serine methyl ester **5** (Scheme 1).

RESULTS AND DISCUSSION

We envision that the Michael-type addition of the chiral bicyclic enolate of **4** to acrylate derivatives is the key step for the synthesis of the HMG skeleton. Toward this aim, we assayed the reaction of

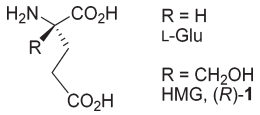
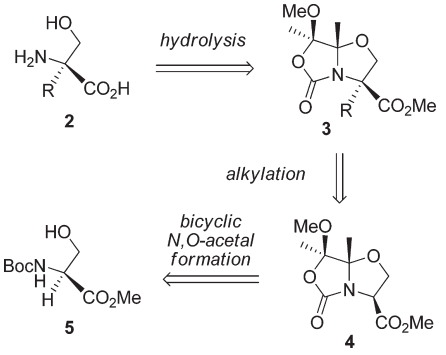


Figure 1. L-Glutamic and (2*R*)-(hydroxymethyl)glutamic acids.

Scheme 1. Retrosynthesis of α-Alkylserine Derivatives 2



bicyclic serine equivalent (3*S*,7*R*,7a*S*)-**4** with methyl acrylate in the presence of KHMDS as a base and using THF as a solvent, at −78 °C. Surprisingly, a diastereoisomeric mixture of compounds (3*S*,6*R*,7a*S*)-**6** and (3*S*,6*S*,7a*S*)-**6** was obtained in a 39:61 ratio, respectively (Scheme 2). The absolute configuration of the major compound (3*S*,6*S*,7a*S*)-**6** was deduced from the X-ray diffraction analysis of the corresponding monocrystal (see Supporting Information).

These compounds were formed by a domino process that involves a Michael addition of the enolate **4′** derived from bicyclic

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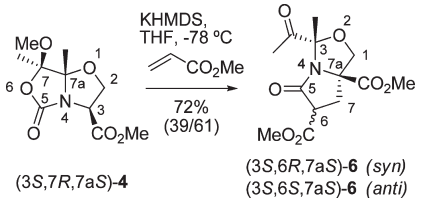
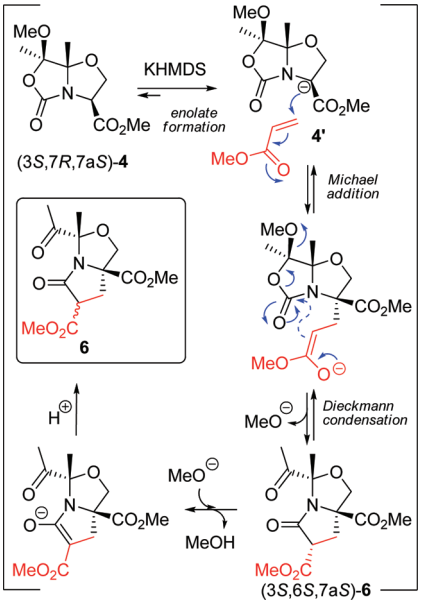
Scheme 2. Domino Michael/Dieckmann Process



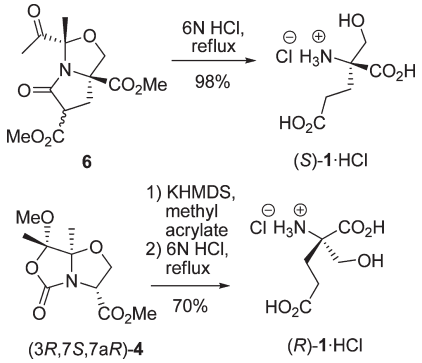
Scheme 3. Proposed Mechanism of the Domino Michael/Dieckmann Process



N,*O*-acetal serine (3*S*,7*R*,7a*S*)-**4** to methyl acrylate, followed by a Dieckmann reaction promoted by the participation of the cyclic carbamate group. A plausible mechanism for this domino process is depicted in Scheme 3. Note that the countercation (K or Li) does not influence the stereochemical outcome of the process, because when we carried out the reaction using LHMDS as a base, we obtained the same results. According to the experimental observation, the low stereoselectivity (60/40) of two epimers at C6 in product **6** is a consequence of the last step of protonation and of the thermodynamic relative stability of both epimers. The reaction should afford a high stereoselectivity in product **6**, which is lost in the deprotonation step by the action of methoxide anion. In fact, we performed the workup of the reaction with ND_4Cl, and the same proportion of deuterated derivatives of **6** was observed.

As an example of the synthetic utility of the above-mentioned domino reaction, we have visualized the synthesis of HMG, since its substructure is included in the skeleton of isomers **6**. In this way, the treatment of diastereoisomeric mixture **6** with 6 N HCl aqueous solution under reflux allowed us to obtain HMG (*S*)-**1** as a hydrochloride derivative. In this easy process, we have carried out five reactions in one pot: the acid hydrolysis of the two methyl ester groups, of the lactam, and of the *N*,*O*-acetal cycles, along with the decarboxylation of one of the carboxylic acid functions in a 1,3-disposition (Scheme 4).

Scheme 4. Synthesis of the HMG (*S*)-1 and (*R*)-1 as Hydrochloride Derivatives



In the same way as that described above for the synthesis of HMG (*S*)-**1**, but starting from the enantiomer of (3*S*,7*R*,7a*S*)-**4**, the bicyclic serine equivalent (3*R*,7*S*,7a*R*)-**4**, which could be obtained from commercially available *N*-Boc-D-serine methyl ester, the HMG (*R*)-**1** was also achieved (Scheme 4).

This high diastereoselectivity experimentally obtained (dr > 20:1), along with the retention of configuration observed, let us propose a highly pyramidalized ester enolate as the true source of this stereodifferentiation. This feature has also been observed in the diastereoselective alkylation of this bicyclic system oriented toward the preparation of α-alkylserines.[10a] In fact, the inversion barrier of this enolate was calculated to be greater than any other process occurring under the reaction conditions. To corroborate this feature, several theoretical calculations at the B3LYP/6-31+G(d) level were made in a manner similar to that previously reported for the diastereoselective alkylation[10a] but now including methyl acrylate as an electrophile (see Computational Details and Supporting Information). The lowest energy barrier of activation ($\Delta G^{\ddagger}$) corresponding to the Michael addition (**ts6**; 20 transition structures calculated, Figure 2) of enolate **4**′ was computed to be only 5.6 kcal mol^{-1} in the gas phase. This energy value was much lower than that (**ts4**′) associated to the epimerization of **4**′ (11.9 kcal mol^{-1}, as described in Supporting Information). These competing transition states became closer in energy when solvent effects were included in the calculations (9.1 and 12.2 kcal mol^{-1} for **ts6** and **ts4**′, respectively), but the nucleophilic addition of the unaltered pyramidalized enolate to the olefin remained as the most favorable process. Following this trend, the calculated pathways of the Michael addition of methyl acrylate by the opposite face of the enolate (**ts6_epi**; 17 transition structures calculated) were highly unfavored, the lowest energy barrier being 12.8 and 16.8 kcal mol^{-1} in the gas phase and in solution, respectively.

As a referee suggested, and despite the much poorer coordinating character of K with respect to other commonly modeled cations such as Li, the K cation, in the presence of explicit solvent, was included in the gas-phase calculations in order to avoid artifacts derived from the naked enolate negative charge. According to our previous results,[10a] the most stable enolate−K ionic pair is a chelate in which the cation is coordinated to the carbonyl of carbamate and methoxycarbonyl groups of enolate **4**′. In this more complex model, K cation was solvated with four dimethyl ether molecules, thus acquiring an octahedral geometry. In addition, not only "open" but also "closed" transition state models, as first proposed by Heathcock[11] et al. and then revisited by Bernardi[12] et al. and more recently by Evans[13] et al. for intermolecular Michael reactions, were calculated. In this particular system, both reactants

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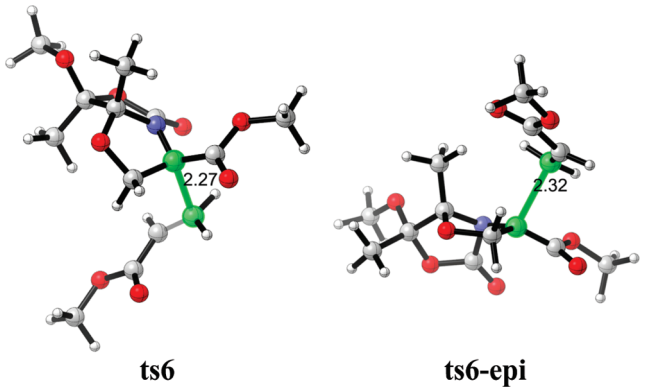


Figure 2. B3LYP/6-31+G(d) minimum energy transition structures for the simple "open" anionic, unsolvated model of the Michael addition reaction between the bicyclic *N*,*O*-acetal **4** and methyl acrylate, yielding major (left) and minor (right) epimers of **6**. Forming C−C bonds are highlighted in green. Distances are given in angstroms.

which take part in the Michael reaction were coordinated to an explicitly modeled K cation, forming an eight-membered TS and thus reducing the reaction entropic cost significantly. In addition to methyl acrylate, three additional dimethyl ether molecules (one has been replaced by the acrylate) were coordinated to K to generate stable octahedral complexes. Multiple position isomers and rotamers for methyl acrylate, and two epimers at the reacting carbon atom, were evaluated both in the reacting complexes (64 optimized structures) and in the transition states (8 optimized structures) (see Supporting Information). The minimum energy transition structures for both approximations of the acrylate in the "open" and "closed" models are depicted in Figure 3.

The presence of the cation reinforces the pyramidal character of the enolate and largely prevents its epimerization (the transition state could not be located in the potential energy surface under these conditions). Because of the charge neutralization and explicit solvation, the minimum energy barriers increase and the effects of implicit solvation are largely reduced, as expected ($\Delta G^{\ddagger}$ = 17.1 and 15.1 kcal mol^{-1} for **ts6_K_open** in the gas phase and in solution, respectively. For the approximation of the acrylate by the unfavored face of the enolate, the minimum energy barrier in the presence of the solvated K cation (**ts6-epi_K_open**) was again much higher (23.9 and 21.4 kcal mol^{-1} in the gas phase and in solution, respectively). Along with this increase in the activation energies, the distances of the incipient C−C bonds are ca. 0.25 Å shorter than those calculated in anionic unsolvated enolates (see Figures 2 and 3). As also observed in the simplest models, the *s*-cis conformation of methyl acrylate is again the most reactive one toward Michael addition.

In line with the referee hypothesis, the energy barriers associated to the analogous "closed" models were significantly lower than those of the "open" ones, but the same complete stereoselectivity was calculated ($\Delta G^{\ddagger}$ = 10.1 and 14.1 kcal mol^{-1} in solution for **ts6_K_closed** and **ts6-epi_K_closed**, respectively). Given that the coordination of the acrylate to the tetrasolvated complex (i.e., forming "closed" complexes from "open" ones) is a slightly exergonic process in solution by ca. 2 kcal/mol, the more realistic "closed" neutral solvated model provides the lowest energy pathway to both major and epimeric Michael adducts (7.8 and 11.8 kcal/mol in THF solution, respectively). These results contribute to validate previous studies performed on simpler systems.[13]

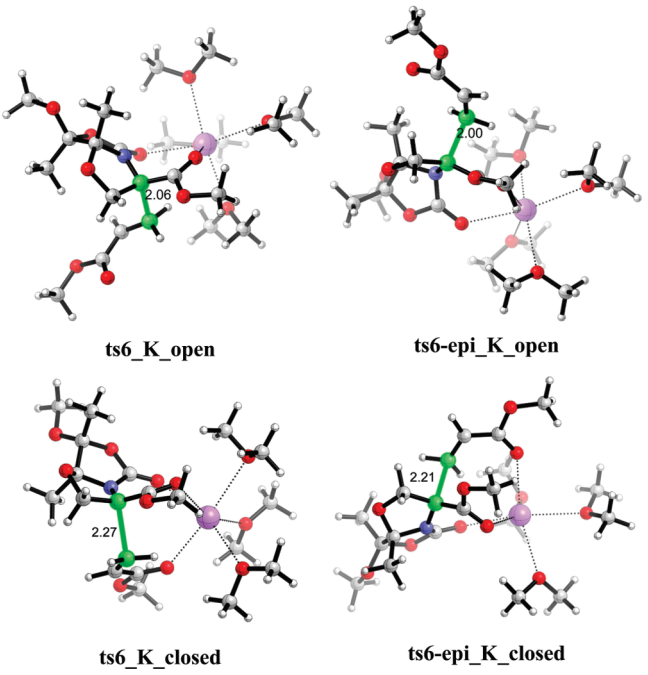


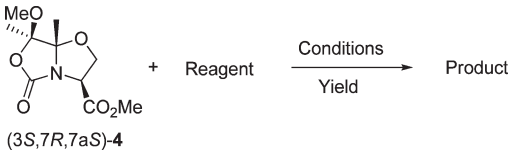
Figure 3. B3LYP/6-31+G(d) minimum energy transition structures for "closed" (lower panel) and "open" neutral solvated (upper panel) models of the Michael addition reaction between bicyclic *N*,*O*-acetal **4** and methyl acrylate, yielding major (left) and minor (right) epimers of **6**. Forming C−C bonds are highlighted in green. Distances are given in angstroms.

As demonstrated through this comprehensive study including several models, the driving force of the complete stereoselectivity achieved in the Michael addition of derivative **4** to α,β-unsaturated carbonyl compounds is, irrespective of the absolute value of the energy barrier, the highly pyramidalized character of the bicyclic enolate moiety along with the structural factors intrinsic to the nature of the whole "closed" chelate arrangement. Given the total agreement achieved between both experimental and theoretical stereoselectivities using both anionic and neutral ("open" and "closed") models and the computational cost of the last one, the simplest model (anionic) was used in the successive calculations performed using different Michael acceptors (vide infra).

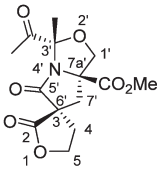
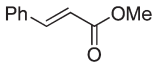
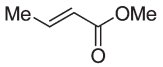
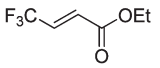
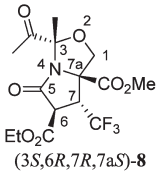
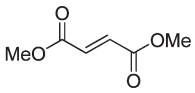
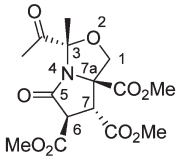
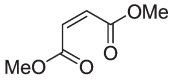
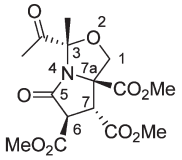
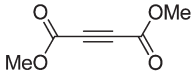
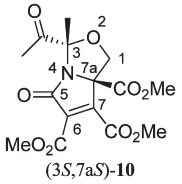
In order to expand the synthetic utility of this domino reaction, we have tested the reactivity of serine equivalent **4** with several α,β-unsaturated esters (Table 1).

Initially, we decide to assay the reaction of chiral building block (3*S*,7*R*,7a*S*)-**4** with a conformationally restricted cyclic acrylate such as 2-methylene-4-butyrolactone, under the same conditions as that described above for methyl acrylate. In this case, we only obtained one product with a good yield, corresponding to spirocyclic derivative (3*S*,3′*S*,7a′*S*)-**7** (entry 1, Table 1). Fortunately, we could establish the absolute configuration of the stereocenters by the X-ray analysis of a monocrystal obtained from slow crystallization of **7**. As in the above case, the stereochemical control of carbon C7a′ proceeds from the highly pyramidalized ester enolate of **4**, while the high diastereoselectivity observed in the carbon C3 arises from the Dieckmann reaction. Thus, the lowest energy barrier calculated for the Michael addition of enolate **4′** to 2-methylene-4-butyrolactone (**ts7**; 10 "open" transition structures located, see Supporting Information) was very similar to that calculated with methyl acrylate and also significantly lower than the inversion barrier of the corresponding

Table 1. Domino Processes between (3*S*,7*R*,7a*S*)-4 and Several α,β-Unsaturated Esters



(3*S*,7*R*,7a*S*)-**4**

Entry	Reagent	Conditions[a]	Product	Yield (%)[b]
1		A	 (3*S*,3'*S*,7a'*S*)-**7**	53
2		A or B	Dimerization product of **4**	--
3		A or B	--	--
4		B	 (3*S*,6*R*,7*R*,7a*S*)-**8**	76
5		A	 (3*S*,6*R*,7*R*,7a*S*)-**9** Accompanied of dimerization product of **4** (60%)	24
6		A	 (3*S*,6*R*,7*R*,7a*S*)-**9**	79
7		B	 (3*S*,7a*S*)-**10**	84

[a] Condition A: Reagent (3.0 equiv), LHMDS (2.0 equiv), THF, −78 °C, 45 min. Condition B: Reagent (3.0 equiv), LHMDS (2.0 equiv), HMPA (4.0 equiv), THF, −78 °C, 45 min. [b] Yields were determined after purification by column chromatography.

enolate: 5.5 and 10.7 kcal mol^{-1} in the gas phase and in THF solution, respectively.

The geminal-disubstituted character of 2-methylene-4-butyrolactone prevents the possibility of deprotonation at C6′ of product **7** by means of a spirocyclic substitution pattern with no acidic hydrogens. As a consequence, the complete stereoselectivity achieved in the Dieckmann cyclization step is preserved. As a tentative explanation of the different diastereoselectivities observed in the multistep formation of the final lactams, the thermodynamic stabilities of both epimers at C6 (in product **6**) and C6′ (in product **7**) positions were calculated (see Supporting Information). In excellent agreement with the experimental ratio, a 37:63 mixture of both diastereomers based on the Boltzmann distribution obtained from the Gibbs free energies of each calculated structure (16 conformers) was found for bicycle **6** in the gas phase (18:82 ratio in THF solution). In the absence of more conclusive experimental evidence, isomer (3*S*,6*S*,7a*S*)-**6** can be proposed as the major product of the global process with methyl acrylate. On the other hand, the

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isomer with the same absolute configuration found in the X-ray structure, namely (3*S*,3′*S*,7a′*S*)-**7**, was calculated to be the only reaction product with 2-methylene-4-butyrolactone (eight conformers, 100:0 ratio in the gas phase, 96:4 ratio in THF solution). The importance of compound **7** is due to the fact that it can be regarded as a chimeric amino acid derivative in which three amino acid substructures are presented; serine, glutamic acid, and pyroglutamic acid.

The next step was to study the behavior of this domino reaction with β-substituted acrylate derivatives. Initially, we carried out the reaction with methyl cinnamate and we did not observe the expected Michael product under any condition tested (entry 2, Table 1). Instead, a dimerization product of the starting material **4** (described in ref 10b) was observed as a consequence of the lack of reactivity of methyl cinnamate. According to the observed inability of methyl cinnamate to undergo the Michael addition in the presence of the potassium enolate, the minimum energy barrier of this process (16 new "open" transition structures) was calculated to be much higher than that of β-unsubstituted acrylic derivatives (14.0 and 20.1 kcal mol^{-1}) in the gas phase and in solution, respectively. Thus, the presence of the phenyl ring deactivates the α,β-unsaturated carbonyl system toward nucleophilic attack of the enolate by means of resonance effects, also providing significant steric hindrance at the β position, increasing the energy barrier in ca. 8 kcal·mol^{-1}.

In the case of methyl crotonate (entry 3, Table 1), we only observed the starting material because the base is consumed in the deprotonation at the γ position (methyl group attached to the double bond). Therefore, a limitation of this domino reaction involves the existence of the acidic protons in the starting materials. To eliminate this handicap, we carried out the reaction with (*E*)-ethyl 4,4,4-trifluorobut-2-enoate (entry 4, Table 1), and compound (3*S*,6*R*,7*R*,7a*S*)-**8** was the only isomer obtained with a good yield. The configuration at C7a was again retained and, in the C6 carbon showed *R*-configuration. In this sense, it is important to note that the stereocenter C3 of compound **7** has the same configuration as stereocenter C6 of compound **8**, although showing *S*-configuration according to the Cahn–Ingold–Prelog priority rules. Moreover, now, a new stereocenter appears (C7) in compound **8**, which showed an *R*-configuration. In summary, the two new stereocenters created in the domino process (C6 and C7) adopt a trans configuration. These features were confirmed by 2D NOESY experiments on compound (3*S*,6*R*,7*R*,7a*S*)-**8** (see Supporting Information).

When we assayed the reaction of **4** with dimethyl fumarate (entry 5, Table 1) and dimethyl maleate (entry 6, Table 1), we observed a difference of reactivity between them. Indeed, while in the second case the yield was good, in the first case the yield of the domino process decreased to 24% because of dimerization of starting material **4**. Nevertheless, the product obtained in both cases was the same, compound (3*S*,6*R*,7*R*,7a*S*)-**9**, which was the only stereoisomer obtained arising from the domino process. The stereochemistry was unambiguously deduced from the X-ray analysis of the corresponding monocrystal of compound **9** (see Supporting Information). Therefore, it is possible to control all three stereocenters created in the domino process starting from the β-substituted acrylate derivative of either cis or trans configuration. The stereochemical outcome of Michael reactions with methyl fumarate and maleate are discussed in the Supporting Information.

Finally, we assayed the domino reaction of **4** with dimethyl acetylenedicarboxylate, and we only obtained the product (3*S*,7a*S*)-**10**, in excellent yield. Again, the stereochemistry at C7a was retained. Obviously, in this case, no stereocenter is created at C6 or C7, but the result obtained is important because this kind of domino process involves alkynes as Michael acceptors. The absolute configuration of the sterocenters was deduced from the 2D NOESY experiments on compound **10** (see Supporting Information).

CONCLUSION

We have carried out a straightforward synthesis of both enantiopure (*S*)- and (*R*)-(hydroxymethyl)glutamic acids by a domino Michael/Dieckmann process followed by acid hydrolysis. The key step, in which the stereocenter is created, involves the Michael addition of the bicyclic enolate to methyl acrylate, which occurs with retention of configuration, as supported by theoretical calculations. The synthetic utility and the scope of this domino process were demonstrated by testing several α- or β-disubstituted acrylate derivatives and even an alkyne Michael acceptor, dimethyl acetylenedicarboxylate. A computational analysis of the Michael addition has been carried out including extensive computations on the chelate transition structures with explicit ethereal solvation.

EXPERIMENTAL SECTION

General Procedures. Solvents were purified according to standard procedures. Column chromatography was performed using silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as internal reference (chemical shifts are reported in ppm on the δ scale, coupling constants in hertz). Assignment of all separate signals in the ^{1}H NMR spectra was made on the basis of coupling constants; ge-COSY and ge-HSQC experiments were performed on a 400 MHz spectrometer. This spectrometer was also used for the 2D NOESY experiments described in the text. These experiments were processed with MestreNova software (Mestrelab Research, Spain). Melting points were determined on a melting point apparatus and are uncorrected. Electrospray mass spectra were recorded on a spectrometer; accurate mass measurements were achieved using sodium formate as an external reference.

(3S,6R,7aS)- and (3S,6S,7aS)-Dimethyl 3-Acetyl-3-methyl-5-oxohexahydropyrrolo[1,2-c]oxazole-6,7a-dicarboxylate ***6***. Bicyclic *N*,*O*-acetal serine (3*S*,7*R*,7a*S*)-**4** (1.304 g, 5.32 mmol) was dissolved in dry THF (130 mL) under an argon atmosphere, and the solution was cooled at −78 °C. Methyl acrylate (1.44 mL, 15.95 mmol) was added by syringe, and then a 1 M solution of KHMDS in THF (10.63 mL) was added dropwise. After the reaction was stirred for 20 min at −78 °C, the crude mixture was quenched with a saturated aqueous NH_4Cl solution (100 mL). The resulting mixture was warmed to room temperature and diluted with diethyl ether (100 mL). The aqueous phase was extracted with more diethyl ether (3 × 20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Solvent evaporation and column chromatography purification on silica gel (hexane/ethyl acetate 6:4) gave diastereoisomeric mixture of (3*S*,6*R*,7a*S*)-**6** and (3*S*,6*S*,7a*S*)-**6** (1.140 g, 3.81 mmol, yield: 72%) as a yellow pale oil in a 39:61 ratio, as determined by ^{1}H NMR. HRMS (ESI) m/z = 322.0911 $(M + Na)^+$; calcd for $C_{13}H_{17}NNaO_7^+$ = 322.0897. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72 (s, 3H), 1.85 (s, 3H), 2.27 (s, 3H), 2.31 (s, 3H), 2.51–2.60 (m, 1H), 2.51–2.60 (m, 1H), 2.84–2.94 (m, 1H), 2.84–2.94 (m, 1H), 3.70–3.73 (m, 1H), 3.75 (s, 3H), 3.69–3.77 (m, 1H), 3.82 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 3.83–3.86 (m, 1H), 4.02 (dd, J = 12.1, 7.7 Hz, 1H), 4.34 (d, J = 9.0 Hz, 1H), 4.57 (d, J = 8.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 21.2, 25.0, 32.8, 33.2, 52.4, 52.4, 52.8, 52.9, 53.1, 53.3, 53.4, 70.6, 72.4, 73.6, 74.4, 93.9, 94.4, 168.2, 168.6, 169.0, 169.0, 172.3, 172.6, 199.2, 199.8.

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(2S)-(Hydroxymethyl)glutamic Acid **1**. Diastereomeric mixture **6** (207 mg, 0.69 mmol) was charged in a round-bottomed flask, and an aqueous solution of 6 N HCl (10 mL) was then added. The reaction was stirred and heated under reflux for 72 h, the solvent was removed in vacuo, and the residue was partitioned between water and ethyl acetate. The aqueous layer was evaporated to give compound **1** (144 mg, 0.67 mmol, 98% yield) as a hydrochloride derivative (**1**·HCl). In order to achieve this amino acid in its free form and to compare its optical activity with those reported in the literature, this product was treated with ethanol/propylene oxide (2:1, 6 mL), under reflux, for 1 h to give **1** as a white solid (25.2 mg 0.14 mmol); yield 21%. $[\alpha]^{25}_{D}$ = +6.4 (*c* = 0.99 in H_2O). The spectroscopic data were identical to those reported in the literature.[2] HRMS (ESI) *m*/*z* = 178.0712 $(M + H)^+$; calcd for $C_6H_{12}NO_5^+$ = 178.0710.

(3R,6S,7aR)- and (3R,6R,7aR)-Dimethyl 3-Acetyl-3-methyl-5-oxohexahydropyrrolo[1,2-c]oxazole-6,7a-dicarboxylate **6**. Following the same methodology as described for diastereoisomeric mixture (3*S*,6*R*,7a*S*)-**6** and (3*S*,6*S*,7a*S*)-**6** but using serine bicyclic *N*,*O*-acetal (3*R*,7*S*,7a*R*)-**4** (63 mg, 0.26 mmol) as starting material, we obtained another diastereoisomeric mixture (3*R*,6*S*,7a*R*)-**6** and (3*R*,6*R*,7a*R*)-**6** (58 mg, 0.19 mmol, yield 75%) as a yellow pale oil with a 60:40 ratio. $[\alpha]^{25}_{D}$ = +24.4 (*c* 0.99 in $CHCl_3$). The spectroscopic data were identical to those described for distereoisomeric mixture (3*S*,6*R*,7a*S*)-**6** and (3*S*,6*S*,7a*S*)-**6**. HRMS (ESI) *m*/*z* = 322.0909 $(M + Na)^+$; calcd for $C_{13}H_{17}NNaO_7^+$ = 322.0897.

(2R)-(Hydroxymethyl)glutamic Acid **1**. Following the same methodology as described for (2*S*)-(hydroxymethyl)glutamic acid **1**, but using diastereoisomeric mixture (3*R*,6*S*,7a*R*)-**6** and (3*R*,6*R*,7a*R*)-**6** (58 mg, 0.19 mmol) as starting material, we obtained (2*R*)-(hydroxymethyl)-glutamic acid **1** in 93% yield as a hydrochloride derivative. In the same way, this product was treated with ethanol/propylene oxide (2:1, 3 mL), under reflux, for 1 h to give (*R*)-**1** as a white solid (25.2 mg 0.14 mmol); yield 28%. $[\alpha]^{25}_{D}$ = −5.8 (*c* = 1.00 in H_2O). The spectroscopic data were identical to those reported for its enantiomer. HRMS (ESI) *m*/*z* = 178.0718 $(M + H)^+$; calcd for $C_6H_{12}NO_5^+$ = 178.0710.

(3S,3′S,7a′S)-Methyl 3′-Acetyl-3′-methyl-2,5′-dioxohexahydro-1′H,2H-spiro[furan-3,6′-pyrrolo[1,2-c]oxazole]-7a′-carboxylate **7**. Bicyclic *N*,*O*-acetal serine (3*R*,7*S*,7a*R*)-**4** (86 mg, 0.36 mmol) was dissolved in dry THF (10 mL) under an argon atmosphere. The solution was cooled at −78 °C. α-Methylene-γ-butyrolactone (94 μL, 1.08 mmol) was added by syringe and then, a 1 M KHMDS solution (0.72 mL) was added dropwise. After the reaction was stirred for 45 min at −78 °C, the crude mixture was quenched with saturated aqueous NH_4Cl solution (10 mL). The resulting mixture was warmed to room temperature and diluted with diethyl ether (10 mL). The aqueous phase was extracted with more diethyl ether (3 × 5 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Solvent evaporation and column chromatography purification on silica gel (hexane/ethyl acetate 1:1) gave compound **7** (59 mg, 0.19 mmol, yield: 53%) as a white solid. HRMS (ESI) *m*/*z* = 312.1079 $(M + H)^+$; calcd for $C_{14}H_{18}NO_7^+$ = 312.1078; $[\alpha]^{25}_{D}$ = +39.7 (*c* 0.98 in $CHCl_3$); mp = 129 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.22−2.30 (m, 1H), 2.32 (s, 3H), 2.43 (d, *J* = 13.1 Hz, 1H), 2.81−2.93 (m, 1H), 3.02 (d, *J* = 13.0 Hz, 1H), 3.72 (d, *J* = 9.1 Hz, 1H), 3.87 (s, 3H), 4.25 (d, *J* = 9.1 Hz, 1H), 4.29−4.40 (m, 1H), 4.50−4.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 25.5, 32.7, 38.8, 53.2, 57.3, 67.1, 70.6, 75.0, 95.1, 171.2, 172.4, 174.7, 199.7.

(3S,6R,7R,7aS)-6-Ethyl 7a-Methyl 3-Acetyl-3-methyl-5-oxo-7-(trifluoromethyl)hexahydro-pyrrolo[1,2-c]oxazole-6,7a-dicarboxylate **8**. Bicyclic *N*,*O*-acetal serine (3*R*,7*S*,7a*R*)-**4** (97 mg, 0.39 mmol) was dissolved in dry THF (10 mL) under an argon atmosphere. The solution was cooled at −78 °C. Ethyl 4,4,4-trifluorocrotonate (177 μL, 1.18 mmol) and HMPA (274 μL, 1.58 mmol) were added by syringe, and a 1 M LHMDS solution (0.79 mL) was then added dropwise. After the reaction was stirred for 45 min at −78 °C, the crude mixture was quenched with saturated aqueous NH_4Cl solution (10 mL). The resulting mixture was warmed to room temperature and diluted with diethyl ether (10 mL). The aqueous phase was extracted with more diethyl ether (3 × 5 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Solvent evaporation and column chromatography purification on silica gel (hexane/ethyl acetate 6:4) gave compound **8** (113 mg, 0.30 mmol, yield: 76%) as a colorless oil. HRMS (ESI) *m*/*z* = 382.1109 $(M + H)^+$; calcd for $C_{15}H_{19}F_3NO_7^+$ = 382.1108; $[\alpha]^{25}_{D}$ = −16.7 (*c* 1.07 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.1 Hz, 3H), 1.83 (s, 3H), 2.30 (s, 3H), 3.85−3.92 (m, 2H), 3.90 (s, 3H), 4.14 (dd, *J* = 9.3, 1.2 Hz, 1H), 4.27 (qd, *J* = 7.1, 3.8 Hz, 2H), 4.33 (d, *J* = 9.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 21.2, 25.5, 45.2 (q, $^2J_{CF}$ = 31.0 Hz), 53.6, 53.8, 63.1, 69.33 (q, $^3J_{CF}$ = 3.2 Hz), 71.3, 94.1, 124.7 (q, $^1J_{CF}$ = 279.5 Hz), 164.8, 166.0, 171.2, 199.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −67.2.

(3S,6R,7R,7aS)-Trimethyl 3-Acetyl-3-methyl-5-oxohexahydropyrrolo[1,2-c]oxazole-6,7,7a-tricarboxylate **9**. Method A: Bicyclic *N*,*O*-acetal serine (3*R*,7*S*,7a*R*)-**4** (112 mg, 0.46 mmol) was dissolved in dry THF (10 mL) under an argon atmosphere. The solution was cooled at −78 °C. Dimethyl maleate (172 μL, 1.37 mmol) was added by syringe, and a 1 M LHMDS solution (0.91 mL) was then added dropwise. After the reaction was stirred for 45 min at −78 °C, the crude mixture was quenched with saturated aqueous NH_4Cl solution (10 mL). The resulting mixture was warmed to room temperature and diluted with diethyl ether (10 mL). The aqueous phase was extracted with more diethyl ether (3 × 5 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Solvent evaporation and column chromatography purification on silica gel (hexane/ethyl acetate 1:1) gave compound **9** (129 mg, 0.36 mmol, yield: 79%) as a white solid. Method B: Following the same procedure but starting from dimethyl fumarate as Michael acceptor olefin, the yield of compound **9** was only 24%. HRMS (ESI) *m*/*z* = 358.1122 $(M + H)^+$; calcd for $C_{15}H_{20}NO_9^+$ = 358.1133; $[\alpha]^{25}_{D}$ = −12.8 (*c* 1.05 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (s, 3H), 2.25 (s, 3H), 3.71 (d, *J* = 9.5 Hz, 1H), 3.77 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 3.99−4.05 (m, 1H), 4.27−4.32 (m, 1H), 4.38 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 25.5, 46.4, 52.9, 53.4, 53.6, 54.7, 71.1, 72.3, 94.0, 166.7, 167.3, 168.7, 171.6, 199.6.

(3S,7aS)-Trimethyl 3-Acetyl-3-methyl-5-oxo-1,3,5,7a-tetrahydropyrrolo[1,2-c]oxazole-6,7,7a-tricarboxylate **10**. Bicyclic *N*,*O*-acetal serine (3*R*,7*S*,7a*R*)-**4** (61 mg, 0.25 mmol) was dissolved in dry THF (10 mL) under an argon atmosphere. The solution was cooled at −78 °C. Dimethyl acetylenedicarboxylate (92 μL, 0.75 mmol) and HMPA (183 μL, 0.99 mmol) were added by syringe, and a 1 M LHMDS solution (0.49 mL) was then added dropwise. After the reaction was stirred for 45 min at −78 °C, the crude mixture was quenched with saturated aqueous NH_4Cl solution (10 mL). The resulting mixture was warmed to room temperature and diluted with diethyl ether (10 mL). The aqueous phase was extracted with more diethyl ether (3 × 5 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Solvent evaporation and column chromatography purification on silica gel (hexane/ethyl acetate 1:1) gave compound **10** (74 mg, 0.21 mmol, yield: 84%) as a colorless oil. HRMS (ESI) *m*/*z* = 378.0796 $(M + Na)^+$; calcd for $C_{15}H_{17}NNaO_9^+$ = 378.0796; $[\alpha]^{25}_{D}$ = −9.8 (*c* 1.07 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.79 (s, 3H), 2.27 (s, 3H), 3.70−3.76 (m, 1H), 3.80 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 4.76 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8, 25.9, 53.1, 53.4, 53.9, 68.8, 74.9, 95.3, 137.2, 145.4, 160.7, 160.7, 167.3, 168.3, 199.8.

Computational Details. Calculations were carried out with the M06-2X[14] and B3LYP[15] hybrid functionals (see Supporting Information) and 6-31+G(d) basis set. The B3LYP widely used functional has been successfully employed in the calculation of Michael conjugate additions involving a broad range of substrates.[16,17] Full geometry optimizations and transition structure (TS) searches were carried out with the Gaussian09 package.[18] The possibility of different position isomers, conformations, and stereoisomers was taken into account for all structures (see Supporting Information). 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 because significant errors in the calculated thermodynamic properties are not found at this theoretical level.[19] The experimental reaction temperature (−78 °C) was considered in the estimation of the thermal and entropic contributions to Gibbs free energies. Calculations were carried out both in the presence and in the absence of K^+ cation neutralizing the enolate negative charge and forming a chelate with the carbonyl of carbamate and methoxycarbonyl groups. Bulk solvent effects were taken into account through the polarized continuum model (IEF-PCM)[20] with radii and nonelectrostatic terms from the SMD solvation model[21] as implemented in Gaussian09. The internally stored parameters for tetrahydrofuran were used to calculate solvation energies (ΔG_{solv}). Up to four explicit solvent (dimethyl ether) molecules surrounding K were included in geometry optimizations when necessary, for which both full QM and hybrid QM/MM (ONIOM)[22] calculations were performed (see Supporting Information). Gibbs free energies (ΔG) were used for the discussion on the relative stabilities of the considered structures. 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.

■ ASSOCIATED CONTENT

Supporting Information. Spectroscopic characterization of all compounds. Complete ref 18. X-ray data of compounds **6**, **7**, and **9** and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Brauner-Osborne, H.; Egebjerg, J.; Nielsen, E.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609–2645. (b) *CNS Neurotransmitter and Neuromodulators: Glutamate*; Stone, T. W., Ed.; CRC Press: Boca Raton, FL, 1995. (c) Moloney, M. G. *Nat. Prod. Rep.* **2002**, *19*, 597–616.

(2) Zhang, J.; Flippen-Anderson, J. L.; Kozikowski, A. P. *J. Org. Chem.* **2001**, *66*, 7555–7559.

(3) (a) Choudhury, P. K.; Le Nguyen, B. K.; Langlois, N. *Tetrahedron Lett.* **2002**, *43*, 463–464. (b) Langlois, N.; Le Nguyen, B. K. *J. Org. Chem.* **2004**, *69*, 7558–7564.

(4) Kawasaki, M.; Namba, K.; Tsujishima, H.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2003**, *44*, 1235–1238.

(5) (a) Lee, J.; Lee, Y.-I.; Kang, M. J.; Lee, Y.-J.; Jeong, B.-S.; Lee, J.-H.; Kim, M.-J.; Choi, J.-Y.; Ku, J.-M.; Park, H.-G.; Jew, S.-S. *J. Org. Chem.* **2005**, *70*, 4158–4168. (b) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Jeong, B.-S.; Lee, J.-H.; Kim, T.-S.; Lee, J.; Ku, J.-M.; Jew, S.-S.; Park, H.-G. *Org. Lett.* **2005**, *7*, 3207–3209.

(6) Battistini, L.; Curti, C.; Zanardi, F.; Rassu, G.; Auzzas, L.; Casiraghi, G. *J. Org. Chem.* **2004**, *69*, 2611–2613.

(7) Tang, G.; Tian, H.; Ma, D. *Tetrahedron* **2004**, *60*, 10547–10552.

(8) (a) Hayes, C. J.; Bradley, D. M.; Thomson, N. M. *J. Org. Chem.* **2006**, *71*, 2661–2665. (b) Miyaoka, H.; Yamanishi, M.; Hoshino, A.; Kinbara, A. *Tetrahedron* **2006**, *62*, 4103–4109. (c) Yiotakis, A.; Magriotis, P. A.; Vassiliou, S. *Tetrahedron: Asymmetry* **2007**, *18*, 873–877. (d) Martinkova, M.; Gonda, J.; Raschmanova, J.; Uhrlkova, A. *Tetrahedron: Asymmetry* **2008**, *19*, 1879–1875.

(9) (a) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **1999**, *64*, 8220–8225. (b) Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 4653–4661. (c) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2195–2204. (d) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2001**, *12*, 949–957. (e) Avenoza, A.; Busto, J. H.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2003**, *14*, 399–405. (f) Avenoza, A.; Busto, J. H.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2004**, *15*, 719–724. (g) Avenoza, A.; Busto, J. H.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Synthesis* **2005**, 575–578.

(10) (a) Aydillo, C.; Jiménez-Osés, G.; Busto, J. H.; Peregrina, J. M.; Zurbano, M. M.; Avenoza, A. *Chem.—Eur. J.* **2007**, *13*, 4840–4848. (b) Jiménez-Osés, G.; Aydillo, C.; Busto, J. H.; Zurbano, M. M.; Peregrina, J. M.; Avenoza, A. *J. Org. Chem.* **2007**, *72*, 5399–5402. (c) Jiménez-Osés, G.; Aydillo, C.; Busto, J. H.; Zurbano, M. M.; Peregrina, J. M.; Avenoza, A. *J. Org. Chem.* **2007**, *72*, 7070–7070. (d) Aydillo, C.; Avenoza, A.; Busto, J. H.; Jiménez-Osés, G.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2008**, *19*, 2829–2834.

(11) (a) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157–172. (b) Oare, D. A.; Heathcock, C. H. Stereochemistry of the Base-Promoted Michael Addition Reaction. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1989; Vol. 19, pp 227—408.

(12) Bernardi, A.; Capelli, A. M.; Cassinari, A.; Comotti, A.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1992**, *57*, 7029–7034.

(13) Kwan, E. E.; Evans, D. A. *Org. Lett.* **2010**, *12*, 5124–5127.

(14) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

(15) (a) Lee, C.; Yang, W.; Parr, R. *Phys. Rev. B* **1988**, *37*, 785–789. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.

(16) See, for instance: (a) Chatfield, D.; Augsten, A.; D'Chuna, C.; Lewandowska, E.; Wnuk, S. *Eur. J. Org. Chem.* **2004**, 313–322. (b) Ilieva, S.; Cheshmedzhieva, D.; Tasheva, D. *Tetrahedron* **2010**, *66*, 5168–5172. (c) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826–832. (d) Fustero, S.; Chiva, G.; Piera, J.; Volonterio, A.; Zanda, M.; González, J.; Morán-Ramallal, A. *Chem.—Eur. J.* **2007**, *13*, 8530–8542. (e) Wei, X.; Zhang, D.; Zhang, C.; Liu, C. *Int. J. Quantum Chem.* **2010**, *110*, 1056–1062. More particularly, the B3LYP/6-31+G(d) method has been previously used in:(f) Lewandowska, E.; Chatfield, D. C. *Eur. J. Org. Chem.* **2005**, 3297–3303.

(17) The accuracy of the B3LYP method has been discussed in a recent work: Rokob, T. A.; Hamza, A.; Pápai, I. *Org. Lett.* **2007**, *9*, 4279–4282. A comparative study of the energetics of the Michael addition reactions described in this work, between the classic B3LYP and the modern M06—2X functional, is available in the Supporting Information.

(18) Frisch, M. J. et al. *Gaussian09, Revision A.02*, Gaussian, Inc., Wallingford, CT, 2009.

(19) Bauschlicher, C. W., Jr. *Chem. Phys. Lett.* **1995**, *246*, 40–44.

(20) (a) Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253–260. (b) Tomasi, J.; Mennucci, B.; Cancès, E. *J. Mol. Struct.* **1999**, *464*, 211–226. (c) Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43—54, and references therein. (d) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999–3093.

(21) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

(22) Svensson, M.; Humbel, S.; Froese, R. D. J.; Matsubara, T.; Sieber, S.; Morokuma, K. *J. Phys. Chem.* **1996**, *100*, 19357–19363.