Articles

Reaction between *N*-Alkylhydroxylamines and Chiral Enoate Esters: More Experimental Evidence for a Cycloaddition-like Process, a Rationale Based on DFT Theoretical Calculations, and Stereoselective Synthesis of New Enantiopure *β*-Amino Acids

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Received July 10, 2001

The reactions between *N*-benzyl- and *N*-methylhydroxylamine and chiral enoate esters, derived from D-glyceraldehyde and (−)-verbenone, respectively, have been investigated. Theoretical calculations show that the most favorable mechanism involves the concerted cycloaddition of the hydroxylamine to the substrate. This result is in good agreement with the stereospecificity observed when the trisubstituted olefins are used. The open-chain adducts have been isolated when the processes are carried out at low temperatures and for short reaction times. These compounds evolve to the corresponding isoxazolidinones on standing at room temperature or under acid catalysis. The high *π*-facial diastereoselection has been rationalized on the basis of steric effects induced by the dioxolane ring for D-glyceraldehyde derivatives or by the cyclobutane *gem*-dimethyl substitution for esters prepared from (−)-verbenone. As an application of these reactions, new *β*-amino acids have been synthesized in a highly efficient and stereocontrolled manner.

Introduction

Since J. E. Baldwin reported in 1984 that the addition of *N*-substituted hydroxylamines to α,*β*-unsaturated esters is a general procedure for the synthesis of isoxazolidin-5-ones,[1] the reaction between *N*-alkylhydroxylamines and conjugated esters,[2−4] lactones,[5,6] or lactams[7] has been employed in the synthesis of isoxazolidinyl nucleoside analogues,[3,4,8] carbapenems,[5a] and *β*-amino acids,[9] among other interesting products. In 1976, H. Stamm[10] studied the addition of *N*-methylhydroxylamine to ethyl crotonate and stated, for the first time, that the process takes place through the 1,4-conjugate addition or Michael-type reaction (Scheme 1, pathway a) of the hydroxylamine to afford a *β*-hydroxyamino ester (**P3**) which was isolated and identified by its spectroscopic data. These authors confirmed the role of such a compound as an intermediate in the isoxazolidinone formation since it spontaneously cyclized on standing for several days in chloroform solution. On the basis of the acidity of *N*-methylhydroxylamine (pK_a 4.6), the addition was believed to occur assisted by the coordination of the hydroxyl proton to the carbonyl.[10] This coordination was also invoked by S. W. Baldwin to explain the stereoselectivity observed in the reactions between (α-methylbenzyl)hydroxylamine and *β*-substituted acrylate esters, where neither the double bond geometry nor the size of the *β*-substituent seemed to have any effect on the diastereoselectivity of the overall process.[2] In that work, it was suggested that the reaction is irreversible since isoxazolidinones do not equilibrate under the reaction conditions (refluxing benzene in the presence of potassium carbonate) and, moreover, pure open-chain intermediates lead to single isoxazolidinones under these conditions.

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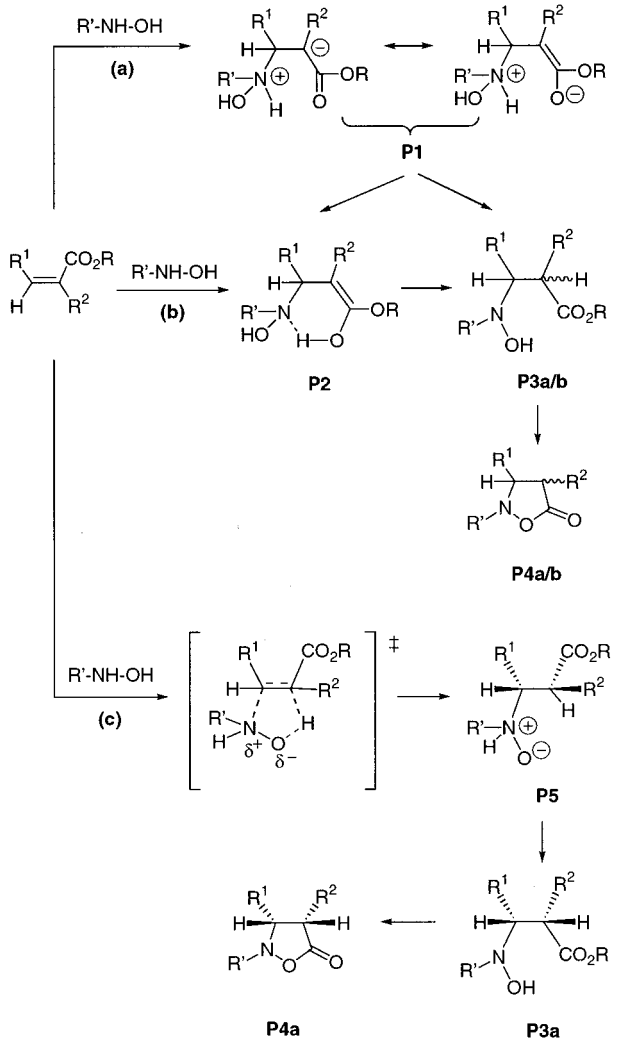
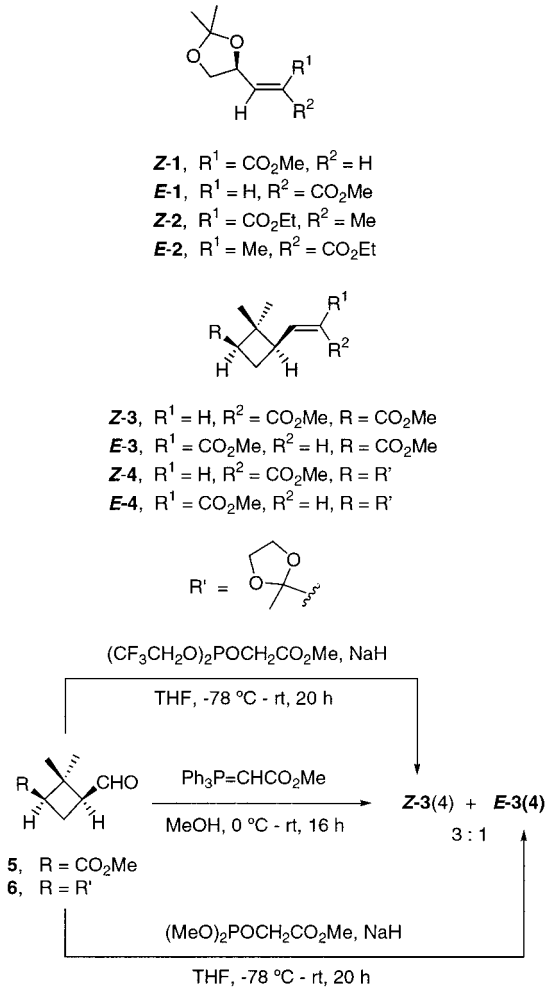
10.1021/jo0159082 CCC: $22.00 © 2002 American Chemical Society
Published on Web 03/16/2002

Scheme 1



Scheme 2

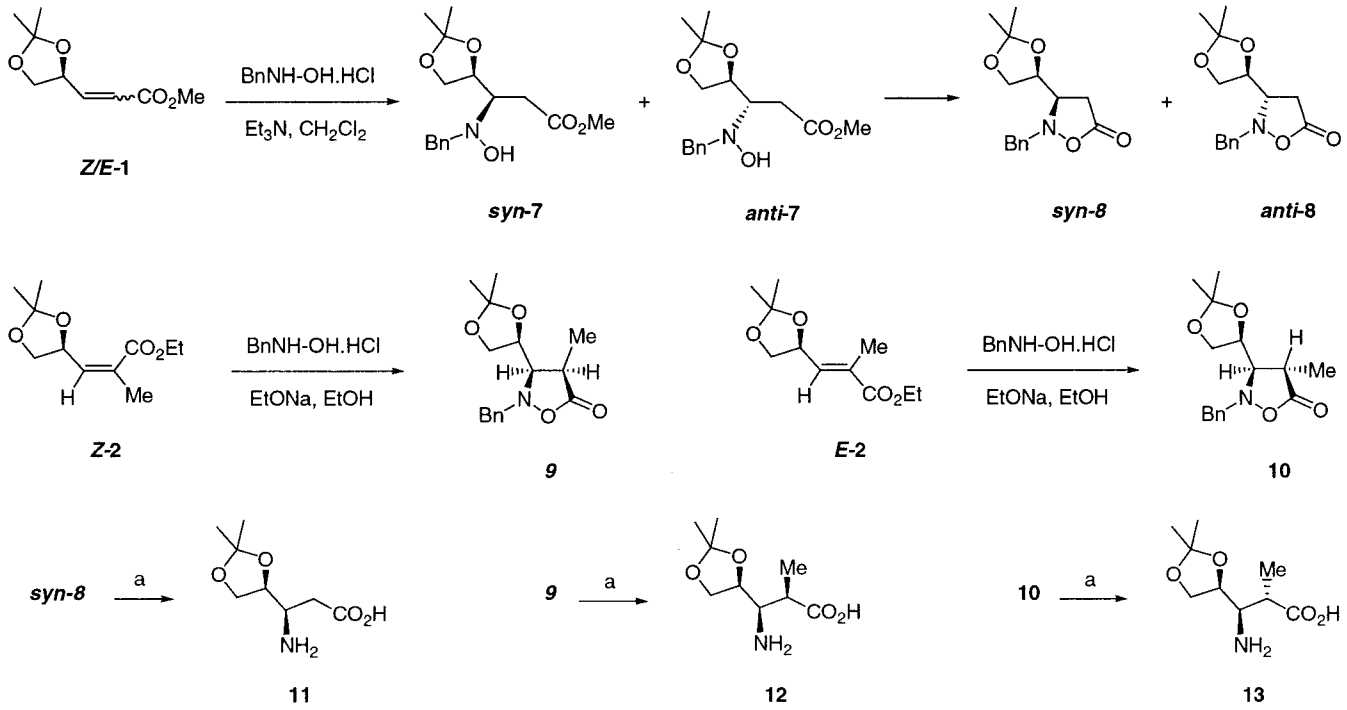


For trisubstituted olefins, if the addition takes place through zwitterion **P1** (Scheme 1, path a) or through intermediate **P2** (path b), the stereoselectivity in the production of hydroxyester **P3** and, consequently, of isoxazolidinone **P4** would be dependent on the stereochemical outcome of the proton-transfer processes. Recently, K. Zhao has postulated a concerted mechanism through a cyclic transition state for the addition of *N*-methylhydroxylamine to conjugated esters (Scheme 1, pathway c). Accordingly, the O*H* proton would be intramolecularly transferred to the α-carbonyl carbon, giving a zwitterion, **P5**, which tautomerizes fast to the corresponding *β*-hydroxyamino ester with retention of the *Z*/*E* configuration of the starting alkene. This hypothesis was supported by elegant deuteration experiments and by the observation that the *Z*/*E* relative stereochemistry remained unaltered in isoxazolidinones when achiral trisubstitued alkenoates were used.[3b]

The combination of its stereocontrolled outcome with the use of chiral substrates or reagents makes this reaction extremely attractive for the stereoselective synthesis of optically pure products of biological interest, and therefore, efforts directed to elucidate the origin of the diastereoselection have been made. When the double bond is located in conformationally constrained cyclic molecules such as unsaturated lactones[5,6] or lactams,[7] the stereochemistry of the major products is easily rationalized as the result of the *anti* attack with respect to the substituent attached to the stereogenic centers already present in the substrates. More difficult is the rationalization and the prediction of the diastereoselection in flexible open-chain molecules. For instance, P. Merino reported the influence on the *π*-facial diastereoselectivity exerted by the *Z*/*E* configuration of the double bond and by the protecting groups of the 1,2-amino alcohol subunit in substrates derived from L-serine.[4] In turn, K. Zhao described the reaction of disubstituted chiral alkenoates, derived from D-glyceraldehyde, with *N*-methylhydroxylamine to give *syn* adducts as major isomers independent of the *Z*/*E* geometry of the double bond.[3a] This result is in agreement with the previous work by S. W. Baldwin.[2] However, the factors determining the stereocontrol have not been systematized.

In this paper, we report our results on the study of the reaction of *N*-alkylhydroxylamines with chiral α,*β*-unsaturated esters to rationalize its mechanism and to establish its scope to produce optically pure isoxazolidinones in a stereocontrolled manner. Thus, the reactions between *N*-benzylhydroxylamine and di- or trisubstituted (*Z*)- and (*E*)-alkenoates (Scheme 2), derived from D-glyceraldehyde and (−)-verbenone, respectively, have been investigated. DFT theoretical calculations have been undertaken to ascertain whether a cycloaddition-like process is more favorable than a two-step mechanism. Moreover, the stereocontrol due to a dioxolane or a cyclobutyl moiety as internal inductor of the *π*-facial diastereoselection has been shown and justified both by

Scheme 3[a]



[a] Reagents and conditions: (a) H_2, $Pd(OH)_2/C$, H_2O/EtOH, 4 atm.

experiments and by calculations. Factors influencing the cyclization of the intermediates have also been explored. Finally, the synthetic usefulness of the obtained chiral isoxazolidinones has been evidenced in the preparation of enantiopure new β-amino acids. These compounds contain one or two new stereogenic centers created in the addition step with determined absolute configuration.

Results and Discussion

1. Reactions between *N*-Benzylhydroxylamine and Alkenoates 1−4. Synthesis of Chiral Oxazolidinones. Alkenoates **1** (*Z*- and *E*-isomers) (Scheme 2) are commercially available. Alternatively, they can be easily synthesized from D-glyceraldehyde through Wittig condensation.[11] Alkenoates **2** (*Z* and *E* isomers) were prepared according to the procedures described in the literature.[12] Condensations of aldehydes **5** and **6**, obtained from (−)-verbenone,[13] with the appropriate phosphonates afforded the new compounds (*Z*)- and (*E*)-**3(4)** as shown in Scheme 2. Thus, reaction of **5** with Still's reagent, $(CF_3CH_2O)_2POCH_2CO_2CH_3$,[14] in the presence of sodium hydride afforded stereoselectively *Z*-isomers of **3** and **4**, repectively, in 60% yield. Alternatively, condensation of **5** with the anion derived from dimethyl (methoxycarbonylmethyl)phosphonate provided *E*-isomers in 55−60% yield. A stereoisomeric mixture resulted from the reactions between aldehyde **5** or **6** and methyl (triphenylphosphoranylidene)acetate, the *E*-isomer being the major product.

In preliminary experiments, dichloromethane solutions of compounds (*Z*)- and (*E*)-**1** were reacted in separate experiments with 1.2 equiv of *N*-benzylhydroxylamine hydrochloride, in the presence of triethylamine. In both cases, the yield and stereoselectivity were similar. Therefore, mixtures of *Z*/*E* olefinic isomers were used in further experiments. β-Hydroxyamino esters **7** (Scheme 3) were the sole products detected when the reaction between **1** and *N*-benzylhydroxylamine was performed at −20 °C overnight. These compounds cyclized smoothly on standing to give isoxazolidinones **8**. For instance, a 5:3.5 mixture of **7** and **8** resulted after 1 day at room temperature, conversion being complete after several days. Attemps to accelerate the cyclization by stirring the mixture in the presence of $ZnCl_2$, as previously described,[4,6] failed. This result is in accordance with that reported by Merino.[4] When the reaction of **1** with *N*-benzylhydroxylamine was performed at room temperature for 17 h, a mixture of isomeric *syn*/*anti*-**7**, contaminated with some amount of **8**, was obtained after the usual treatment (see the Experimental Section).[15] Chromatography on silica gel afforded the isoxazolidinones *syn*-**8** and *anti*-**8** as the only products which were fully characterized. We concluded that acid silica gel catalyzed, therefore, the cyclization of **7** into **8**. On the contrary, chromatography on neutral Baker silica allowed the isolation of *syn*-**7** and *anti*-**7**, which were characterized by their spectroscopic data.

In these reactions, the yield of the adducts was 75−90% and the *syn*/*anti* ratio was about 10:1 as determined by HPLC and ^{1}H NMR analysis of the reaction crudes.

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(15) In contrast with the results previously reported by Zhao,[3a] examination of the crude resulting from the reaction of (*Z*)-**1** with *N*-methylhydroxyalmine at room temperature for 17 h, performed in our laboratory, revealed the presence of the corresponding oxazolidinone (as a 10:1 *syn*/*anti* mixture) as the only product (89% yield), the open-chain β-hydroxylamino esters not being detected by careful ^{1}H NMR analysis.

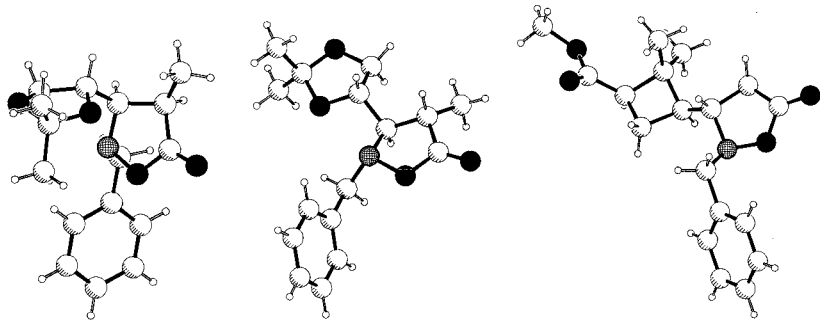
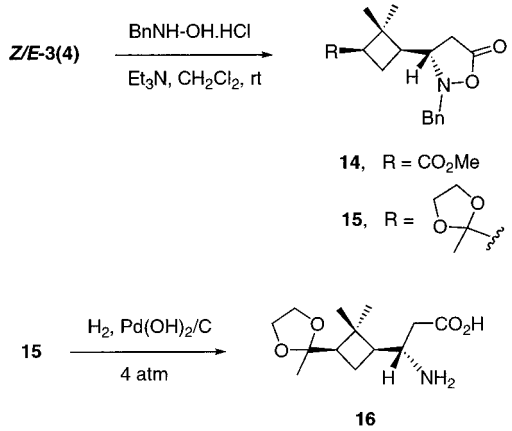


Figure 1. Structures of compounds **9**, **10**, and **14** as determined by X-ray structural analysis.

Scheme 4



The *syn* configuration was assigned to the major diastereoisomer according to our previous experience on the predominant π-facial diastereoselection involved in other cycloaddition reactions of these alkenoates,[16] and in agreement with the results reported by Zhao on the reactions of **1** with *N*-methylhydroxylamine.[3a]

Trisubstituted olefins **2** did not react under the conditions described above for the parent compound **1**. Nevertheless, stereospecific additions were accomplished under more energetic conditions. Thus, (*Z*)-**2** was made to react with *N*-benzylhydroxylamine hydrochloride in the presence of excess sodium ethoxide in boiling ethanol for 15 h. After column chromatography on silica gel, crystalline isoxazolidinone **9** was obtained in 59% yield, in a single *syn* isomeric form, as the only defined product. Similarly, the diastereomeric compound **10** was synthesized from (*E*)-**2** in 55% yield. The configuration of these compounds was assigned by X-ray structural analysis (Figure 1), showing the excellent stereocontrol in the creation of the new stereogenic centers.

The reactions of cyclobutyl alkenoates **3** and **4** were also explored. *E* isomers reacted faster than *Z* ones, but both stereoisomers converged into isoxazolidinones **14** and **15**, respectively (65−70% yield), by treatment with *N*-benzylhydroxylamine in dichloromethane at room temperature overnight (Scheme 4). Open-chain intermediates were not detected. The configuration of **14** was established by X-ray analysis (Figure 1) and can be rationalized as the result of a preferential orientation of the attack on the (C_2-*re*)-face of the double bond induced by the *gem*-dimethyl substitution of the cyclobutane (Figure 2). This π-facial diastereoselection has also been observed in the cycloaddition of diazomethane to other related cyclobutyl alkenoates and rationalized on the basis of conformational bias for these molecules.[17] By extension, the configuration of **15** was assigned as depicted in Scheme 4.

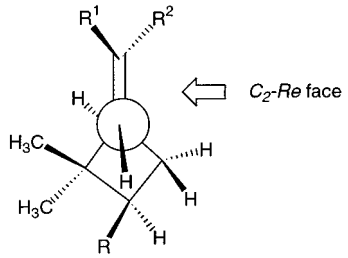


Figure 2. Newman projection for the active conformers related to unsaturated esters **3** and **4**. The arrow marks the preferential attack of the hydroxylamine on the double bond. See also ref 17.

2. Stereoselective Synthesis of β-Amino Acids. Isoxazolidinones **8**−**10**, and **15**, are precursos to new enantiopure β-amino acids through hydrogenolysis of the N−O bond concomitant to the benzyl group removal. Thus, hydrogenation of *syn*-**8** by using palladium hydroxide on charcoal as catalyst, in 7:1 H_2O/EtOH, under 4 atm of pressure, afforded product **11** in 90% yield. In a similar manner, hydrogenation of **9** and **10** produced almost quantitatively the α-methyl-β-amino acids **12** and **13**, respectively, as hygroscopic solids (Scheme 3). Finally, catalytic hydrogenation of **15** provided the γ-cyclobutyl-β-amino acid **16** in 90% yield (Scheme 4).

In this way, reactions of *N*-benzylhydroxylamine with several chiral enoates and subsequent N−O reduction resulted in an efficient method to synthesize stereoselectively different types of β-amino acids.

3. Theoretical Calculations. a. Reaction of Hydroxylamine with Methyl Acrylate. Calculations have been done according to the procedures described in the Computational Details of the Experimental Section. First, we have studied the attack of hydroxylamine on methyl acrylate (MA) as a model system. Figure 3 and Table 1

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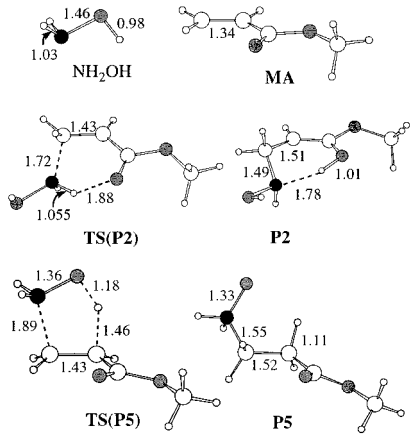

Figure 3. Optimized geometries of the stationary points corresponding to the reaction between hydroxylamine and MA. Selected interatomic distances are in angstroms.

Table 1. Relative Energies and Thermodynamical Parameters at 298.15 K and 1 atm for the Stationary Points Corresponding to the Reaction of NH_2OH with Methyl Acrylate

struct[a]	ΔE^b	ΔH^b	ΔS^c	$\Delta G^{b,d}$
TS(P2)	17.8	18.5	−41.8	31.0 (31.0)
P2	6.5	8.3	−42.1	20.9 (20.9)
TS(P5)	11.1	10.2	−43.0	23.0 (20.6)
P5	1.6	3.7	−40.8	15.9 (12.0)

[a] See Figure 3. [b] In kcal mol^{-1}. [c] In cal K^{-1} mol^{-1}. [d] In parentheses are given the values in CH_2Cl_2 solution ($\epsilon = 8.93$).

summarize the results obtained. We have optimized the geometries of **P2** (Scheme 1, pathway b) and **P5** (pathway c). The formation of these products takes place in one step through transition states **TS(P2)** and **TS(P5)**, respectively. The transition vector of **TS(P2)** shows that the main component of the reaction coordinate is the formation of the C−N bond. On the other hand, the main component of the transition vector of **TS(P5)** is the proton transfer from the OH group of hydroxylamine to the olefin. Table 1 shows that the formation of **P5** is kinetically much more favorable than the formation of **P2**. Moreover, when the effect of solvation by CH_2Cl_2 is taken into account in the gas-phase optimized geometries, the preference for the formation of **P5** is further increased. We have also tried to optimize the geometry of several conformers of the zwitterionic intermediate **P1** (Scheme 1, pathway a), but all attempts failed, even when the effect of solvation by CH_2Cl_2 was considered in the geometry optimization. All these results agree with the concerted mechanism postulated by Zhao[3b] (Scheme 1, pathway c). Consequently, this is the only mechanism that we have considered for the reactions of (*Z*)-**1** and (*E*)-**1**.

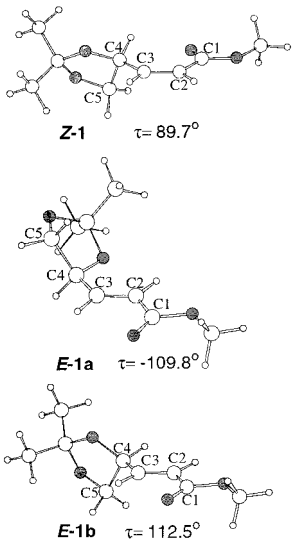

Figure 4. Optimized geometries of the *Z* and *E* isomers of alkenoate **1**. τ is the C1−C2−C3−C4 dihedral angle.

b. Reactions of Hydroxylamine and *N*-Methylhydroxylamine with Alkenoates (*Z*)-1 and (*E*)-1. Figure 4 presents the optimized geometries of (*Z*)-**1** and (*E*)-**1**. We have considered several conformations arising from the rotation around the C1−C2 and C3−C4 bonds. In both geometric isomers, an *s-cis* arrangement of the carbonyl group is the preferred one. Regarding the rotation around C3−C4, for (*Z*)-**1** there is only one energy minimum in which the C4−H bond is nearly eclipsed with the C3−C2 double bond. On the other hand, two different conformational minima have been located for (*E*)-**1**. In the most stable one ((*E*)-**1a**) the C3−C2 double bond is eclipsed with the C4−O bond. The other conformer **(**(*E*)-**1b**) is only 0.2 kcal mol^{-1} higher in energy than (*E*)-**1a**, and it presents a C4−H eclipsed arrangement, similar to the one corresponding to (*Z*)-**1**.

We have located the transition states corresponding to the *syn* and *anti* attacks of hydroxylamine and *N*-methylhydroxylamine on (*Z*)-**1** and (*E*)-**1**. For (*E*)-**1**, we have considered the attack of hydroxylamine on conformers **a** and **b**. In all cases, the lower-energy transition-state structures correspond to the attack on (*E*)-**1b**.

Table 2 presents the values of selected geometry parameters of the transition states, potential energy barriers, and activation thermodynamic parameters for the reactions of hydroxylamine and *N*-methylhydroxylamine with (*Z*)-**1** and (*E*)-**1**. The structures of the transition states for the reactions of *N*-methylhydroxylamine are shown in Figure 5.

The values of the potential energy barriers show that for (*Z*)-**1** the *syn* attack is slightly preferred over the *anti*

Table 2. Selected Geometry Parameters,[a] Potential Energy Barriers, and Activation Thermodynamical Parameters at 298.15 K and 1 atm for the Transition States Corresponding to the Reactions of R−NH−OH with (*Z*)-1 and (*E*)-1

R	TS[b]	C3−N	C2−H	O−H	τ[c]	ω[d]	$\Delta E^{\ddagger}$ThinSpace[e]	$\Delta H^{\ddagger}$ThinSpace[e]	$\Delta S^{\ddagger}$ThinSpace[f]	$\Delta G^{\ddagger}$ThinSpace[e]
H	Z-syn	1.88	1.45	1.19	82.3	−1.3	11.0	10.0	−44.2	23.2
	Z-anti	1.86	1.50	1.16	67.7	−9.5	11.3	10.8	−50.7	25.9
	E-syn	1.87	1.48	1.18	89.8	6.8	9.9	9.0	−44.2	22.2
	E-anti	1.88	1.52	1.15	60.5	−7.3	11.3	10.7	−47.6	24.9
Me	Z-syn	1.88	1.45	1.19	81.3	5.4	9.4	8.5	−46.6	22.4
	Z-anti	1.86	1.52	1.15	67.3	−13.3	9.7	9.3	−53.0	25.1
	E-syn	1.84	1.51	1.15	86.7	13.7	7.6	7.0	−45.9	20.7
	E-anti	1.87	1.57	1.12	61.2	−12.3	9.1	9.0	−49.9	23.9

[a] Distanes are in angstroms and dihedral angles in degrees. [b] See Figure 5. [c] C5−C4−C3−C2 dihedral angle. [d] C2−C3−N−O dihedral angle. [e] In kcal mol^{-1}. [f] In cal K^{-1} mol^{-1}.

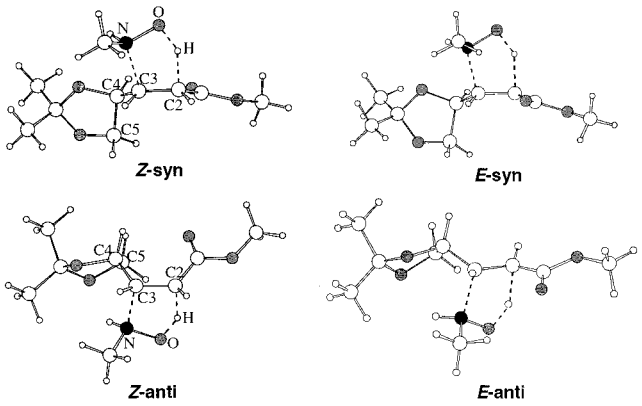

Figure 5. Optimized geometries of the transition states of the reactions of *N*-methylhydroxylamine with (*Z*)-**1** and (*E*)-**1**.

one. This preference is augmented when activation Gibbs energies are considered. Regarding the reactions of (*E*)-**1**, the potential energy barriers are also lower for the *syn* attack, but the energy difference between the *syn* and *anti* transition states is larger than those corresponding to (*Z*)-**1**. In this case, the preference for the *syn* attack also increases when activation Gibbs energies are considered.

Therefore, in all cases, the *syn* attack is kinetically the most favorable one, in excellent agreement with the selectivity experimentally observed. Moreover, the *E* isomer is predicted to be slightly more reactive than the *Z* isomer.

The analysis of the geometries of the transition states shows that the C3−N bond distance only slightly changes from one case to another, whereas more significant differences are observed for the C2−H and H−O distances. The values of these two distances show that the degree of proton transfer for the *syn* transition states is larger than for the *anti* transition states. Since this proton transfer is the main contribution to the transition vector, the *syn* transition states appear later along the reaction coordinate than the *anti* ones.

When the hydroxylamine molecule approaches the olefin, steric repulsions between both fragments come into play. One way to relieve this repulsion is the rotation around the C3−C4 bond. The comparison between the values of the τ torsion angle at the olefin equilibrium geometries (Figure 4) and at the transition states (Table 2) shows that the change of this torsion angle is larger for the *anti* transition states than for the *syn* ones, thus showing than the *anti* attack is more sterically demanding than the *syn* attack. The presence of the methyl group in *N*-methylhydroxylamine does not seem to have a relevant effect. Regarding the ω torsion angle, Table 2 shows that there are deviations from planarity. The presence of the methyl group of *N*-methylhydroxylamine leads to larger torsion angles. For (*Z*)-**1** the torsion around C3−N moves the hydroxylamine O atom toward the ester group, whereas for (*E*)-**1**, the O atom is moved away from the ester group. This different behavior of both geometrical isomers can be related to the pyramidalization of C2. Figure 6 presents side views of the transition states corresponding to the reactions of *N*-methylhydroxylamine with (*Z*)-**1** and (*E*)-**1**. The pyramidalization can be related to the deviation of the ϕ_C and ϕ_H dihedral angles with respect to the planar situation (angles about

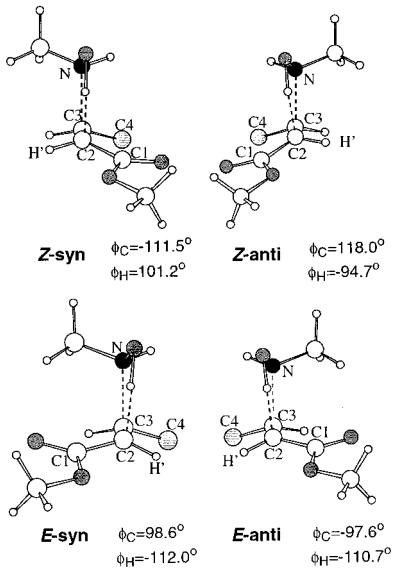

Figure 6. Side views of the transition states of the reactions of *N*-methylhydroxylamine with (*E*)-**1** and (*E*)-**1**. The dioxolane group has been omitted for clarity. ϕ_C and ϕ_H correspond to the N−C3−C2−C1 and N−C3−C2−H′ dihedral angles, respectively.

±90°) corresponding to the equilibrium geometry of the reactants. Figure 6 shows that pyramidalization involves mainly the variation of the dihedral angle corresponding to the group *cis* with respect to dioxolane. In this way, for the *Z* transition states the attack of the proton takes place from the same side as the ester group, whereas for the *E* transition states the attack is produced from the other side.

Concluding Remarks

We have studied by means of theoretical calculations different mechanistic pathways for the addition of hydroxylamine to methyl acrylate. The results obtained point out that the most favorable mechanism involves a concerted process through a cyclic transition state. This result is in agreement with the stereospecificity observed for additions of *N*-alkylhydroxylamines to olefinic substrates.

Low temperatures favor the formation of open-chain adducts which evolve to isoxazolidinones by heating or during chromatography on acid silica gel. When chiral alkenoates are used, an excellent π-facial diastereoselection has been observed and rationalized. Consequently, chiral isoxazolidinones have been synthesized from trisubstituted olefins in a highly stereocontrolled manner. These compounds are useful synthetic precursors to enantiomerically pure new β-amino acids. This feature has been illustrated herein with several examples.

Experimental Section

Alkenoates **1**[11] and **2**[12] (*Z* and *E* isomers) as well as aldehydes **5** and **6**[13] were prepared according to the procedures described in the literature. Flash column chromatography was carried out on silica gel (240−400 mesh). Baker silica (40 μm) was used for the chromatography of acid-sensitive products. Melting points were determined on a hot stage and are uncorrected. Standard ^{1}H NMR and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively. Chemical shifts

in NMR spectra are given on the δ scale. Electron impact MS and HRMS spectra were recorded at 70 eV.

Computational Details. All calculations have been done using density functional (DFT) methods within the generalized gradient approximation (GGA). Molecular geometries have been fully optimized using Becke's[18] functional for exchange and the correlation functional due to Perdew and Wang[19] (BPW91). Molecular geometries have been fully optimized at this level of calculation using the standard 6-31G(d) basis set.[20] Harmonic vibrational frequencies have been calculated for all structures to characterize them as energy minima (all frequencies are real) or transition states (one and only one imaginary frequency). These calculations have been done with the Gaussian-98 program.[21] Single-point calculations have been done for the previously optimized geometries using an uncontracted Slater-type orbital (STO) triple-ζ basis set supplemented with a set of d polarization functions for C, N, and O, and with a set of p functions for H (TZP). These calculations have been done using the ADF program.[22] The reported energy barriers have been calculated with the TZP basis set, whereas zero-point and thermal corrections to the energy and entropies have been calculated from frequencies computed with the 6-31G(d) basis set. For the reaction between hydroxylamine and methyl acrylate, the effect of solvation by CH_2Cl_2 ($\epsilon = 8.93$) has been taken into account at the BPW91/6-31G(d) level of calculation using the conductor-like screening model[23] implemented in the Gaussian-98 program.

Reaction of *N*-Benzylhydroxylamine with 1: Isoxazolidinones 8 through Hydroxyamino Esters 7. *N*-Benzylhydroxylamine hydrochloride (132 mg, 0.8 mmol) and dry triethylamine (120 μL, 0.9 mmol) were successively added to a solution of a *Z*/*E* mixture of alkenoates **1** (129 mg, 0.7 mmol) in anhydrous dichloromethane (4.5 mL). The resulting mixture was stirred at room temperature overnight, under a nitrogen atmosphere. Then, water was added (14 mL), the layers were separated, and the aqueous one was extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was removed at reduced pressure. The residue was chromatographed on silica gel (dichloromethane) to afford 134 mg (70% yield) of a 10:1 mixture of isomeric *syn*/*anti*-**8** as determined by ^{1}H NMR and HPLC (Backerbond column; 3:2 hexane/ethyl acetate; UV detection, $\lambda = 233$ nm). Chromatography on silica gel by using 3:1 hexane/ethyl acetate as eluent afforded fractions of pure *syn*- and *anti*-**8**, which were fully characterized. Hydroxyamino esters *syn*- and *anti*-**7** could be isolated when the reaction was performed at −20 °C overnight, and after solvent removal, the residue was chromatographed on Baker silica (3:1 hexane/ethyl acetate). These compounds led, on standing at room temperature, to the corresponding isoxazolidinones **8**.

Isomeric products **7** were characterized by their ^{1}H NMR ($CDCl_3$) spectroscopic data as follows: *syn*-**7**, 1.36 (s, 3H), 1.40 (s, 3H), 2.47 (dd, $J = 15.5$ Hz, $J' = 4.8$ Hz, 1H), 2.76 (dd, $J = 15.5$ Hz, $J' = 4.8$ Hz, 1H), 3.52 (m, 1H), 3.68 (s, 3H), 3.79 (m, 1H), 3.97 (s, 2H), 3.99 (dd, $J = 7.7$ Hz, $J' = 5.7$ Hz, 1H), 4,44 (m, 1H), 5.00 (br s, 1H), 7.30 (br s, 5 H); *anti*-**7**, 1.32 (s, 3H), 1.37 (s, 3H), 2.63 (dd, $J = 15.6$ Hz, $J' = 5.4$ Hz, 1H), 2.89 (dd, $J = 15.6$ Hz, $J' = 7.9$ Hz, 1H), 3.37 (m, 1H), 3.69 (s, 2H), 3.90 (dd, $J = 8.6$ Hz, $J' = 5.5$ Hz, 1H), 4.10 (dd, $J = 8.6$ Hz, $J' = 6.2$ Hz, 1H), 4.27 (m, 1H), 4.75 (br s, 1H), 7.30 (br s, 5H).

Data for (3*R*,4′*S*)-2-*N*-Benzyl-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1,2-isoxazolidin-5-one, *syn*-8: crystals; mp 71−74 °C; $[\alpha]_D$ +152.3 (*c* 1.08, $CHCl_3$); UV λ_{max} 234 nm, ϵ 710 cm^{-1} M^{-1}; IR (KBr) 1778, 1602, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.33 (s, 3H), 1.41 (s, 3H) 2.57 (dd, $J = 17.2$ Hz, $J' = 8.9$ Hz, 1H), 2.65 (dd, $J = 17.2$ Hz, $J' = 8.1$ Hz, 1H), 3.51 (m, 1H), 3.69 (dd, $J = 8.5$ Hz, $J' = 6.5$ Hz, 1H), 4.01 (dd, $J = 8.5$ Hz, $J' = 6.5$ Hz, 1H), 4.13 (d, $J = 14.0$ Hz, 1H), 4.18 (m, 1H), 4.31 (d, $J = 14.0$ Hz, 1H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) 173.3, 134.9, 129.5, 128.6, 128.0, 110.3, 76.6, 66.0, 65.6, 63.2, 32.3, 26.4, 25.1. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.00, H, 6.68; N, 5.00.

Data for (3*S*,4′*S*)-2-*N*-Benzyl-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1,2-isoxazolidin-5-one, *anti*-8: crystals; mp 88−90 °C; $[\alpha]_D$ −67.3 (*c* 1.07, $CHCl_3$); UV λ_{max} 232 nm, ϵ 804 cm^{-1} M^{-1}; IR (KBr) 1773, 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.29 (s, 3H), 1.35 (s, 3H), 2.69 (dd, $J = 18.0$ Hz, $J' = 5.0$ Hz, 1H), 2.77 (dd, $J = 18.0$ Hz, $J' = 6.9$ Hz, 1H), 3.42 (m, 1H), 3.53 (dd, $J = 8.4$ Hz, $J' = 5.0$ Hz, 1H), 4.00−4.16 (complex absorption, 2H), 4.11 (d, $J = 13.2$ Hz, 1H), 4.24 (d, $J = 13.2$ Hz, 1H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) 175.5, 134.2, 129.6, 128.8, 128.5, 109.9, 75.5, 67.0, 64.1, 63.2, 30.3, 26.5, 24.8. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.30, H, 7.17; N, 4.76.

Reaction of *N*-Benzylhydroxylamine with Alkenoates (*Z*)-2 and (*E*)-2: Isoxazolidinones 9 and 10. A mixture of (*Z*)-**2** (229 mg, 1.1 mmol), *N*-benzylhydroxylamine hydrochloride (851 mg, 5.3 mmol), and sodium ethoxide (363 mg, 5.3 mmol) in absolute ethanol (7 mL) was heated to reflux overnight. Then the mixture was cooled to room temperature, and the solvent was removed at reduced pressure. The residue was dissolved in dichloromethane (10 mL) and washed with water (10 mL). The organic phase was dried ($MgSO_4$), and the solvent was evaporated. The residue was chromatographed on silica gel (3:1 hexane/ethyl acetate) to afford isoxazolidinone **9** (181 mg, 60% yield). In a similar manner, isoxazolidinone **10** was obtained from (*E*)-**2** in 52% yield.

Data for (3*R*,4*R*,4′*S*)-2-*N*-Benzyl-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-4-methyl-1,2-isoxazolidin-5-one, 9: crystals; mp 128−130 °C (dichloromethane/pentane); $[\alpha]_D$ +132.7 (*c* 1.01, $CHCl_3$); UV λ_{max} 232 nm, ϵ 682 cm^{-1} M^{-1}; IR (KBr) 1778, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.30 (d, $J = 7.3$ Hz, 3H); 1.32 (s, 3H), 1.43 (s, 3H), 2.92 (m, 1H), 3.33 (dd, $J = 8.2$ Hz, $J' = 5.0$ Hz, 1H), 3.69 (dd, $J = 8.0$ Hz, $J' = 7.0$ Hz, 1H), 3.94 (dd, $J = 8.0$ Hz, $J' = 6.7$ Hz, 1H), 4.18 (m, 1H), 4.20 (d, $J = 13.5$ Hz, 1H), 4.34 (d, $J = 13.5$ Hz, 1H), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) 177.4, 135.0, 129.3, 128.4, 127.7, 109.9, 76.5, 66.0, 65.8, 62.7, 36.7, 26.1, 25.5, 10.2. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 65.93; H, 7.18; N, 4.83.

Data for (3*R*,4*S*,4′*S*)-2-*N*-Benzyl-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-4-methyl-1,2-isoxazolidin-5-one, 10: crystals; mp 79−81 (dichloromethane/pentane); $[\alpha]_D$ +158.0 (*c* 1.03, $CHCl_3$); UV λ_{max} 232 nm, ϵ 734 cm^{-1} M^{-1}; IR (KBr) 1767, 1652, 1252 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.25 (d, $J = 7.0$ Hz, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 2.77 (m, 1H), 3.17 (dd, $J = 10.9$ Hz, $J' = 7.0$ Hz, 1H), 3.78 (m, 1H), 4.04 (d, $J = 14.3$ Hz, 1H), 4.06 (dd, $J = 8.2$ Hz, $J' = 6.1$ Hz, 1H), 4.23 (m, 1H), 4.57 (d, $J = 14.3$ Hz, 1H). 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) 175.3, 135.3, 129.4, 128.4, 127.9, 109.8, 76.6, 73.2, 65.9, 63.3, 39.9, 26.3, 25.3, 13.9. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 65.81; H, 7.26; N, 4.82.

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General Procedures for the Synthesis of Alkenoates 3 and 4 from Aldehydes 5 and 6, Respectively. Standard protocols are described. Method A: A solution of the aldehyde (2.8 mmol) in methanol or THF (10 mL) was added, at 0 °C, to methyl (triphenylphosphoranylidene)acetate (1.2 g, 3.36 mmol) under a nitrogen atmosphere. The mixture was then stirred at room temperature for 15 h. After evaporation of the solvent, the residue was extracted with boiling hexane (50 mL), filtered, concentrated, and purified by column chromatography. Method B: To a stirred suspension of sodium hydride (100 mg, 2.5 mmol, 60% in mineral oil) in dry THF (2 mL) was slowly added bis(2,2,2-trifluorethyl) (methoxycarbonylmethyl)phosphonate (0.52 mL, 2.5 mmol) under a nitrogen atmosphere. The mixture was cooled to −78 °C, and a solution of aldehyde **5** (200 mg, 1.01 mmol) in THF (2 mL) was added. The resulting mixture was then stirred at room temperature for 10 h. The reaction mixture was treated with a saturated solution of ammonium chloride and then extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed at reduced pressure. The crude product was purified by chromatography (3:2 hexane/ether) to afford 150 mg (60%) of (*Z*)-**3**. Method C: To a suspension of sodium hydride (100 mg, 2.5 mmol, 60% in mineral oil) at −78 °C was added, slowly and with stirring, trimethyl phosphonacetate (455 mg, 2.5 mmol) in dry THF (6 mL) under a nitrogen atmosphere. After 30 min a solution of aldehyde **5** (400 mg, 2.02 mmol) was added. The mixture was then stirred at room temperature for 20 h. The reaction mixture was treated with a saturated solution of ammonium chloride and then extracted with dichloromethane (3 × 30 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed at reduced pressure. The crude product was purified by chromatography (3:2 hexane/ether) to afford 260 mg (50%) of (*E*)-**3**.

Data for Methyl (1′*R*,3′*R*)-3-[2′,2′-Dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]-(*Z*)-2-propenoate, (*Z*)-3: oil; $[\alpha]_D$ −74.91 (*c* 2.75, MeOH); IR (film) 2953, 1725,1650 cm^{-1}; ^1H NMR (acetone-d_6) 1.06 (s, 3H), 1.13 (s, 3H), 1.17 (s, 3H), 1.80 (complex absorption, 1H), 2.00 (m, 2H), 2.22 (dd, J = 11.0 Hz, J' = 8.0 Hz, 1H), 3.64 (s, 3H), 3.70−4.00 (m, 4H), 5.75 (dd, J = 11.7 Hz, J' = 1.1 Hz, 1H), 6.22 (dd, J = 11.7 Hz, J' = 10.2 Hz, 1H); ^{13}C NMR (acetone-d_6) 17.57, 22.76, 24.77, 30.82, 39.94, 43.72, 49.69, 49.89, 63.08, 64.81, 109.04, 119.36, 150.15, 165.65. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.04; H, 8.82.

Data for Methyl (1′*R*,3′*R*)-3-[2′,2′-Dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]-(*E*)-2-propenoate, (*E*)-3: oil; [α] −15.60 (*c* 2.1, MeOH); IR (film) 2954, 1724, 1638 cm^{-1}; ^1H NMR (acetone-d_6) 0.99 (s, 3H), 1.15 (s, 3H), 1.17 (s, 3H), 1.90 (complex absorption, 1H), 2.05 (m, 1H), 2.25 (dd, J = 9.5 Hz, J' = 9.2 Hz, 1H), 2.55 (m, 1H), 3.66 (s, 3H), 3.80−4.00 (m, 4H), 5.75 (dd, J = 15.6 Hz, J' = 1.3 Hz, 1H), 6.89 (dd, J = 15.6 Hz, J' = 7.4 Hz, 1H); ^{13}C NMR (acetone-d_6) 18.68, 23.96, 31.29, 44.33, 45.44, 50.63, 51.41, 64.27, 66.02, 110.04, 121.81, 149.84, 166.91. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.93; H, 8.63.

Methyl (1′*R*,3′*R*)-3-(2′,2′-Dimethyl-3′-methoxycarbonylcyclobutyl)-(*E*)-2-propenoate, 4. This compound was obtained by method A and purified by chromatography (3:1 CH_2Cl_2/AcOEt): yield 342 mg (54%); oil; $[\alpha]_D$ −9.82 (*c* 1.12, $CHCl_3$); IR (film) 2954, 1792, 1734, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) 0.87 (s, 3H), 1.21 (s, 3H), 2.05 (m, 1H), 2.25 (m, 1H), 2.55−2.75 (m, 2H), 3.63 (s, 3H), 3.69 (s, 3H), 5.75 (dd, J = 15.6 Hz, J' = 1.3 Hz, 1H), 6.87 (dd, J = 15.6 Hz, J' = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 18.53, 23.09, 29.82, 44.35, 44.90, 45.80, 51.24, 51.41, 121.62, 147.95, 166.73, 172.78. Anal. Calcd for $(C_{12}H_{18}O_4)_2 \cdot H_2O$: C, 61.25; H, 8.14. Found: C, 61.22; H, 8.07.

Reaction of *N*-Benzylhydroxylamine with 3 and 4: Isoxazolidinones 14 and 15. *N*-Benzylhydroxylamine hydrochloride (400 mg, 2.42 mmol) and dry triethylamine (0.5 mL, 3.75 mmol) were successively added to a solution of a *Z*/*E* mixture of alkenoates **3** or **4** (1.97 mmol) in anhydrous dichloromethane (15 mL). The resulting mixture was stirred at room temperature for 60 h, under a nitrogen atmosphere. Then, water was added (40 mL), the layers were separated, and the aqueous one was extracted with dichloromethane (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was removed at reduced pressure. The residue was chromatographed on silica gel (2:1 hexane/AcOEt) to afford pure compounds.

Data for (3*S*,1′*S*,3′*R*)-2-*N*-Benzyl-3-[2′,2′-dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]-1,2-isoxazolidin-5-one, 14: yield 580 mg (87%); crystals; mp 42−43 °C (hexane/AcOEt); $[\alpha]_D$ −69 (*c* 2.0, MeOH); IR (film) 2930, 1782,1638 cm^{-1}; ^1H NMR (acetone-d_6) 1.07 (s, 3H), 1.16 (s, 3H), 1.19 (s, 3H), 1.65 (m, 1H), 2.00 (m, 2 H), 2.20 (m, 2H), 2.42 (dd, J = 17.2 Hz, J' = 8.2 Hz, 1H), 2.97 (dd, J = 17.2 Hz, J' = 7.3 Hz, 1H), 3.75−3.95 (m, 4H), 4.07 (d, J = 14.0 Hz, 1H), 4.18 (d, J = 14.0 Hz, 1H), 7.30−7.36 (complex absorption, 5H); ^{13}C NMR (acetone-d_6) 17.63, 23.96, 24.17, 31.80, 35.44, 41.78, 46.10, 50.60, 63.77, 64.21, 65.97, 66.92, 110.05, 128.27, 129.03, 129.87, 137.71, 175.16. Anal. Calcd for CHNO: C, 69.54; H, 7.88; N, 4.05. Found: C, 70.04; H, 7.89; N, 3.96.

Data for (3*S*,1′*S*,3′*R*)-2-*N*-Benzyl-3-(2′,2′-dimethyl-3′-methoxycarbonylcyclobutyl)-1,2-isoxazolidin-5-one, 15: yield 311 mg (50%); crystals; mp 78−80 °C (MeOH/H_2CCl_2/hexane); $[\alpha]_D$ −66.01 (*c* 2.0, H_2CCl_2); IR (film) 2954, 1780,-1733 cm^{-1}; ^1H NMR ($HCCl_3$) 0.91 (s, 3H), 1.22 (s, 3H), 2.00−2.20 (m, 3 H), 2.40 (dd, J = 17.1 Hz, J' = 8.5 Hz, 1H), 2.70 (dd, J = 17.0 Hz, J' = 7.2 Hz, 1H), 3.64 (s, 3H), 3.35 (m, 1H), 4.02 (d, J = 14.0, 1H), 4.10 (d, J = 14.0, 1H), 7.32 (complex absorption, 5H); ^{13}C NMR ($CHCl_3$) 17.78, 24.01, 30.37, 35.06, 42.36, 44.85, 45.84, 63.31, 65.97, 127.99, 128.58, 129.06, 135.20, 172.59, 174.10; HRMS *m*/*z* calcd for $C_{18}H_{23}NO_4$ 317.1627, found 317.1632 (M^+).

General Procedure for the Hydrogenolysis of Isoxazolidinones *syn*-8, 9, 10, and 15: *β*-Amino Acids 11, 12, 13, and 16. A standard reaction is described as follows for the reduction of *syn*-**8** to afford **11**. A mixture of isoxazolidinone *syn*-**8** (111 mg, 0.4 mmol) and 20% $Pd(OH)_2$/C (28 mg) in ethanol (10 mL) was hydrogenated at room temperature under 4 atm of pressure. The reaction mixture was filtered through Celite, and the solvent was removed at reduced pressure. The residue was dissolved in 15:2 water/ethanol and filtered through a reversed-phase C_{18}-cartridge eluting with water. After solvent removal, amino acid **11** (68 mg, 90% yield) was obtained. Following the same procedure, amino acids **12**, **13**, and **16** were prepared in nearly quantitative yield.

Data for (3*R*,4′*S*)-3-Amino-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)propanoic Acid, 11: highly hygroscopic solid unsuitable for mp and microanalysis determinations; $[\alpha]_D$ +40.2 (*c* 2.01, methanol); IR (KBr) 3500−3200 (br), 1730, 1295 cm^{-1}; ^1H NMR (methanol-d_4) 1.44 (s, 3H), 2.38 (dd, J = 16.9 Hz, J' = 8.7 Hz, 1H), 2.49 (dd, J = 16.9 Hz, J' = 4.5 Hz, 1H), 3.46 (m, 1H), 3.88 (dd, J = 11.7 Hz, J' = 9.0 Hz, 1H), 4.22 (m, 2H), 4.99 (br s, 2H); ^{13}C NMR (methanol-d_4) 176.5, 111.5, 76.7, 67.4, 53.5, 36.1, 26.8, 25.3; MS *m*/*z* (rel intens) 190 (M^+ + 1, 1), 174 (6), 114 (10), 88 (100), 70 (35), 43 (44).

Data for (2*R*,3*R*,4′*S*)-3-Amino-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-methylpropanoic Acid, 12: deliquescent solid unsuitable for mp and microanalysis determinations; $[\alpha]_D$ +9.2 (*c* 1.95, methanol); IR (KBr) 3421, 1726, 1268 cm^{-1}; ^1H NMR (methanol-d_4) 1.28 (d, J = 7.5 Hz, 3H), 1.45 (s, 3H), 1.52 (s, 3H), 2.50 (m, 1H), 3.46 (dd, J = 7.9 Hz, J' = 4.5 Hz, 1H), 3.83 (m, 1H), 4.34 (m, 2H), 5.02 (br s, 2H); ^{13}C NMR (methanol-d_4) 180.8, 111.2, 75.7, 67.8, 57.1, 41.7, 26.8, 25.6, 12.8; MS *m*/*z* (rel intens) 204 (M^+ + 1, 6), 188 (8), 102 (100), 84 (62), 72 (31), 43 (26).

Data for (2*S*,3*R*,4′*S*)-3-Amino-3-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-methylpropanoic Acid, 13: deliquescent solid unsuitable for mp and microanalysis determinations; $[\alpha]_D$ −11.8 (*c* 1.87, methanol); IR (KBr) 3430, 1721, 1276 cm^{-1}; ^1H NMR (methanol-d_4) 1.37 (d, J = 7.5 Hz, 3H), 1.44 (s, 3H), 1.53 (s, 3H), 2.45 (m, 1H), 3.24 (dd, J = 7.9 Hz, J' = 4.5 Hz, 1H), 3.90 (m, 1H), 4.34 (m, 2H), 5.09 (br s, 2H); ^{13}C NMR (methanol-d_4) 180.6, 111.3, 75.75, 67.77, 58.34, 41.32, 26.78, 25.33, 16.00; MS *m*/*z* (rel intens) 204 (M^+ + 1, 1), 188 (6), 102 (100), 84 (61), 91 (35), 72 (28), 43 (34).

Data for (3*S*,1′*S*,3′*R*)-3-Amino-3-[2′,2′-dimethyl-3′-(2-methyl-1,3-dioxolan-2-yl)cyclobutyl]propanoic Acid, 16: yield 95%; crystals; mp 85−87 °C (EtOH); $[\alpha]_D$ −26.09 (*c* 1.15, MeOH); IR (film) 3543, 2952,1706 cm^{-1}; ^1H NMR (methanol-d_4) 1.20 (s, 3H), 1.28 (s, 3H), 1.30 (s, 3H), 1.80−2.10 (m, 3H), 2.10−2.30 (m, 2H), 2.49 (dd, J = 16.9 Hz, J' = 3.0 Hz, 1H), 3.33 (dd, J = 9.8 Hz, J' = 2.9 Hz, 1H), 3.85−4.10 (m, 4H); ^{13}C NMR (methanol-d_4) 17.09, 23.09, 23.98, 32.06, 38.84, 41.94, 45.37, 50.21, 52.40, 64.67, 66.43, 110.64, 177.63; HRMS *m*/*z* calcd for $C_{13}H_{23}NO_4$ 257.1627, found 257.1631 (M^+).

Acknowledgment. E.M. thanks the Ministerio de Educación, Spain, for a predoctoral fellowship, and A.G.M. thanks the CONICET, Argentina, for a grant. This work has been financially supported by DGESIC and AECI (Spain) and Fundación Antorchas (Argentina) through Projects PB97-0214, Q2812001B, and A-1362211-70, respectively. Computer time from the Centre de Supercomputació de Catalunya is gratefully acknowledged.

Supporting Information Available: Total energies and geometries of energy minima and transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0159082