Diastereofacial Selectivity in the Cycloaddition of Nitrones to (*E*)-γ-Oxygenated α,β-Unsaturated Esters

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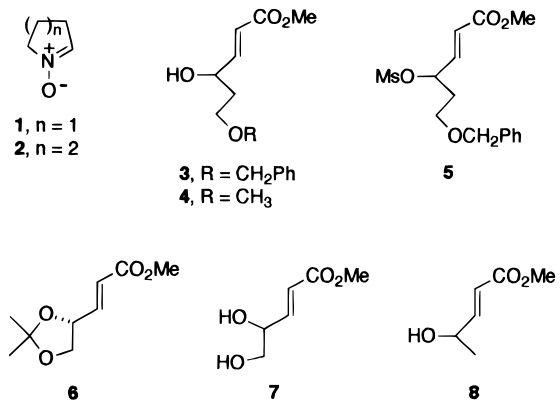
The 1,3-dipolar cycloadditions of nitrones **1** and **2** to a series of 1,2-disubstituted electron-deficient olefins bearing an allylic stereocenter, **4**−**8**, are reported. The *syn*/*anti* stereochemistry of the major *endo* adducts may be rationalized through the Houk transition-state model, but the possibility of intramolecular hydrogen bonding must be taken into account. In the case of the minor *exo* adducts the *syn* stereochemistry always predominates.

Introduction

The synthesis of 4,5-dihydroisoxazoles (Δ^2-isoxazolines) and tetrahydroisoxazoles (isoxazolidines) through intra- and intermolecular 1,3-dipolar cycloadditions of alkenes to nitrile oxides and nitrones, respectively, has been the subject of much research during recent years.[1] When using olefins with a chiral center at the allylic position as the dipolarophile component of the cycloaddition process, one can achieve control of the relative stereochemistry of the new stereogenic centers of the heterocycle in relation to the original allylic atom. To rationalize the stereochemical outcome of nitrile oxide cycloadditions to allylic ethers and alcohols, Houk *et al.*[2] developed a transition-state model that was later extended to nitrone cycloadditions. According to this model, the *inside alkoxy* and the *outside alcohol effects* are responsible for the predominance of *anti* and *syn* stereochemistries of the cycloadducts starting with allylic ethers and alcohols, respectively: with the OH group in the *outside* position the hydrogen bonding with the oxygen atom of the dipole is maximized. A large number of reported studies describe intermolecular reactions between chiral terminal olefins bearing an electronegative atom (O, N, S) at the allylic position and nitrile oxides[1c,2a,c,3] or nitrones,[1c,4] but most published work related to reactions between these dipoles and 1,2-disubstituted olefins with an allylic stereocenter describes intramolecular cycloadditions.[2c,d,5] Published examples dealing with intermolecular cycloaddition reactions between such olefins and nitrile oxides[6−8] or nitrones[6,9,10] are scarce and appeared only very recently.

Chart 1



The influence of allylic substituents in determining the facial selectivity in 1,3-dipolar cycloadditions has also been studied recently for other dipoles such as azomethine ylides[6,11] and diazo compounds.[12]

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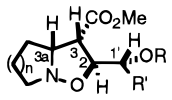
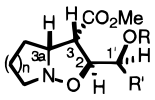
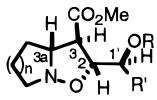
Table 1. Isolated Yields in the Cycloadditions of Nitrones 1 and 2 to Olefins 3−8[24]



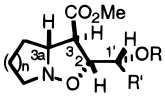
a, *endo-anti*



b, *endo-syn*



c, *exo-anti*



d, *exo-syn*

entry	nitrone	olefin	*endo-anti* (%)	*endo-syn* (%)	*exo-anti* (%)	*exo-syn* (%)
1[10]	**1**	**3**	**9a** (60)	**9b** (22)	traces	
2	**1**	**5**	**10a** (59)	**10b** (18)	traces	
3[10]	**1**	**6**	**11a** (70)	**11b** (14)	traces	
4	**1**	**7**	**12a** (34)	**12b** (49)	traces	
5	**1**	**8**	**13a** (28)	**13b** (57)	traces	
6[10]	**2**	**3**	**14a** (52)	**14b** (22)	**14c** (4)	**14d** (14)
7	**2**	**4**	**15a** (44)	**15b** (23)	**15c** (traces)	**15d** (10)
8	**2**	**5**	**16a** (48)	**16b** (20)	**16c** (8)	**16d** (12)
9	**2**	**6**	**17a** (50)	**17b** (26)	**17c** (5)	**17d** (12)
10	**2**	**7**	**18a** (35)	**18b** (42)	**18c** (4)	**18d** (13)
11	**2**	**8**	**19a** (33)	**19b** (37)	**19c** (5)	**19d** (19)

We have recently described[10] the reactions of nitrones **1** and **2** (Chart 1) with methyl (*E*)-6-(benzyloxy)-4-hydroxy-2-hexenoate (**3**) that were found to be *anti* stereoselective, contrary to the prediction of Houk's model. To explain this unexpected result we considered two hypotheses: the formation of an intramolecular hydrogen bond masks the hydroxyl group in **3**, and consequently, this olefin behaves like an ether, or the presence of a benzyl moiety in **3** gives rise to π stacking interactions[13] in the transition state controlling the steric course of the reaction. To seek some insight into the problem, we decided to carry out the cycloadditions of nitrones **1** and **2** to several (*E*)-γ-oxygenated α,β-unsaturated esters **4**−**8**, which were chosen to evaluate the factors influencing the steric course of the reaction. We report herein the results of the stereochemical outcome of these cycloaddition reactions. As shown, Houk's transition-state model can now be extended to the formation of adducts derived from 1,2-disubstituted olefins through both *endo* and *exo* transition states. The decisive influence of intramolecular hydrogen bonding in the olefin in the steric course of the cycloaddition is also demonstrated.

Results and Discussion

For the purpose of this work we decided to utilize cyclic nitrones **1**[14] and **2**,[15] which we had already used as dipoles in front of several (*Z*)-α,β-unsaturated lactones.[16] With these nitrones, which are incapable of *E*/*Z* isomerization, one can directly relate the stereochemistry of the products to the *endo*/*exo* selectivity of the cycloaddition process, provided that the reaction is conducted under conditions of kinetic control.

Olefin **4** was selected as one of the dipolarophiles to preclude the potential π stacking effect of the aromatic ring in alkene **3**. Oxidation of methyl 6-methoxy-2-hexenoate[17] with selenium dioxide afforded the new compound **4** in 57% yield along with the corresponding γ-oxo derivative. To avoid the formation of intramolecular hydrogen bonding and as an ether analogue of **3**, we selected the mesylate **5**.[18] Olefins **6**[19] and **7**[11a,20] were also included in this study because the subunit 3-butene-1,2-diol and the corresponding ketal have been extensively incorporated in dipolarophile structures.[3a,c,4d,5b,c,6,11a] Finally, methyl 4-hydroxy-2-pentenoate (**8**) was chosen because it is an allylic alcohol unable to form an intramolecular hydrogen bond. Although several methods have been described in the literature for the synthesis of **8**[21] in both racemic and enantiopure form, we have prepared this compound through a different procedure that involves reduction of the known methyl (*E*)-4-oxo-2-pentenoate.[22]

The results of the cycloadditions of nitrones **1** and **2** to olefins **3**−**8** are summarized in Table 1. All the cycloadditions were regioselective, affording cycloadducts with the ester group attached to the 4-position of the isoxazolidine (Chart 2).[1,16,23] The NMR data for all the adducts are consistent with the expected regiochemistry, since the β-carbonylic proton H-2 resonates in all the cycloadducts **9**−**19** at lower fields than the α-carbonylic proton H-3.

In all the reactions of nitrone **1** we isolated only two cycloadducts in overall yields of about 85%. Both adducts are derived from *endo* transition states, although traces of *exo* compounds were detected by ^{1}H NMR analysis of some chromatographic fractions. The *cis* relationship between H-3 and H-3a for adducts **9**−**13** can be deduced from the large values of $J_{3,3a}$ that move in the narrow range 7.5−8.2 Hz. The analysis of molecular models shows that these protons are almost eclipsed in the *endo* adducts but practically orthogonal in the *exo* derivatives. This assignment is reinforced by NOE experiments on compounds **9a** and **11a**[10] and by chemical correlation for adduct **13a** (*vide infra*).

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Chart 2

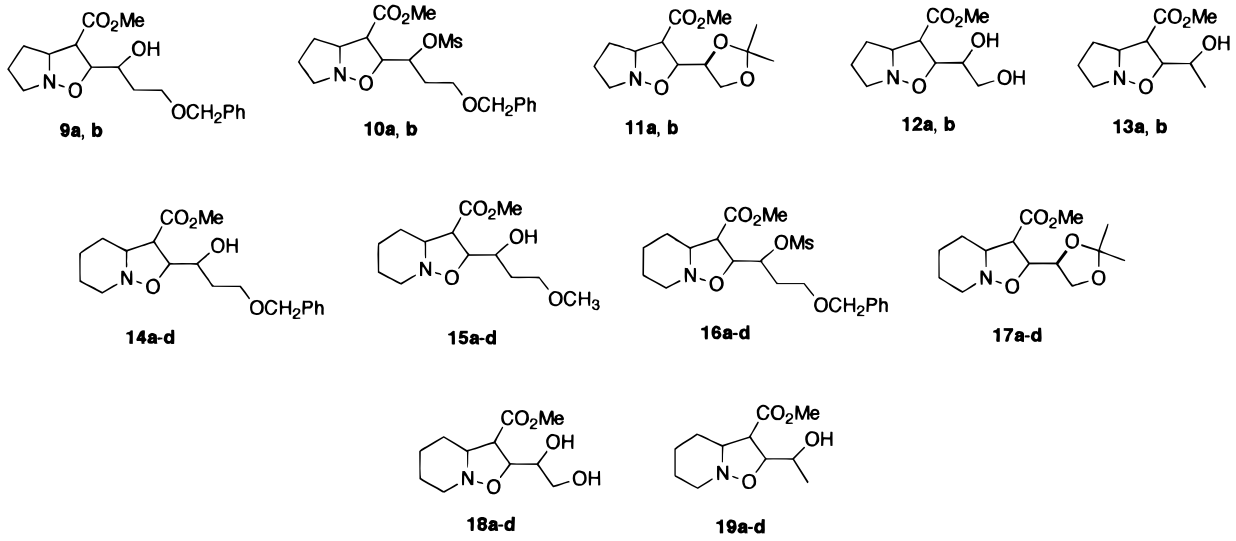
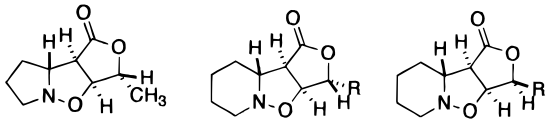


Chart 3



The assignment of the relative configuration at C-2/C-1′ [24] of **11a** and **11b** was based on literature data for related ketal adducts.[3a,c,4d,5b,c,10] In such compounds, it has been observed that the chemical shift value for H-2 and H-1′ always increases on passing from *anti*, **11a**, to *syn*, **11b**, while the value of $J_{2,1'}$ decreases in the same sequence. For diols **12a** and **12b** the chemical shift value for H-2 increases and for H-1′ decreases on passing from *anti*, **12a**, to *syn*, **12b**.[4d] Since in this case the observed differences are very small, we carried out an additional experiment, namely the acid hydrolysis of acetonide **11a**, which gave diol **12a**, validating the previous assignments. The stereochemistry of **13a** was unequivocally established as *endo-anti* by its conversion into the known tricyclic compound **20**[16b] (Chart 3). This transformation was accomplished through epimerization of the α-carbonylic proton of **13a** by treatment with NaH in THF at rt. For the other hydroxylic pair (**9a**,**b**) an identical trend is observed as for **13a,b** on the values of δ H-2, δ H-1′, $J_{2,1'}$, δ C-2 and δ C-1′ on passing from the first eluted to the more polar adduct. Finally, each alcohol **9a** and **9b** was converted separately into the corresponding mesylates **10a** and **10b**.

The reactions of nitrone **2** with olefins **3**−**8** afforded four diastereoisomers in each case. The NMR spectra of some of these adducts at room temperature show broad absorptions due to the slow nitrogen inversion of the perhydroisoxazolo[2,3-*a*]pyridine ring.[16a] Therefore, some spectra were registered at lower temperatures and the *cis* and *trans* invertomers could be observed separately. In all the stereoisomers of **14**−**19** the *trans* invertomer predominates (≥85%).

For each cycloaddition, we assigned the *exo* stereochemistry to the two less polar and minor adducts, since they all present $J_{3,3a}$ values of about 10 Hz, while the *endo* adducts show $J_{3,3a}$ *ca.* 8.4 Hz.[10] This assignment is reinforced by ^{13}C NMR data: in the *trans* invertomers the absorptions of C-3, C-3a, and C-4 are upfield shifted in the *endo* with respect to the corresponding *exo* isomers, as a consequence of their position relative to the pseudoaxial carbonyl group at C-3.[16a]

The *syn*/*anti* assignment of the major *endo* adducts could be unambiguously established for all compounds **14**−**19**. The determination of this relative stereochemistry in products **14a** and **14b** was done by independent chemical correlation of each isomer with the previously reported lactones **21a** and **21b** (Chart 3) derived from *exo-anti* and *exo-syn* transition states, respectively.[10,16a] The great concordance of the NMR data of **14a,b** with those of **15a,b** allowed us to assign the stereochemistry of this last pair. The stereochemistry of the mesylates **16a,b** could be assessed preparing them individually from each alcohol **14a,b** and that of the series **19** through analogy with **14** and **15**. The *syn*/*anti* assignment of compounds **17a,b** and **18a,b** was based on the abovementioned trend of several significant NMR data. Moreover, in an analytical experiment, ketalization of **18a** gave the isomer **17a**.

The elucidation of the *syn*/*anti* stereochemistry of two of the minor adducts, luckily coming from different cycloaddition reactions, namely compounds **15d** and **16d**, could be assured, by X-ray diffraction analyses, as *exo-syn* in both cases.[25] Since all alcohols **14** were independently transformed into the corresponding mesylates **16**, the relative stereochemistry of **14d** was also secured as *exo-syn*. The NMR data for the ketal pair **17c,d** are consistent enough with those of closely related compounds previously reported[3a,c,4d,5b,c,10] and do allow the assignment of their *syn*/*anti* stereochemistry. At this point, we have to consider a general trend observed in the polarity of the compounds so far assigned: the *anti*-isomer is always less polar than the *syn*-isomer, and this rule applies to cycloadducts derived from nitrones **1** or **2** and from both *endo* or *exo* transition states. Therefore, among the *exo* adducts obtained in the reactions between **2** and alcohols **7** and **8**, those more polars, namely **18d**

(24) The numbering 1′, although unsystematic for cycloadducts containing the dioxolane ring, refers to the general formulas in Table 1, and its use assists the discussion of the results. Systematic numbering has been utilized in the Experimental Section.

(25) The authors have deposited atomic coordinates for **15d** and **16d** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

and **19d**, should be *exo-syn*. This stereochemical assignment is reinforced considering the geometry of the transition state (*vide infra*).

All the cycloadditions were run under conditions of kinetic control, since no reequilibration was ever observed when the isolated products were subjected to the reaction conditions. Therefore, it is obvious that the *endo* transition states are favoured over the *exo* in all cases. This observation is in agreement with previously reported results on cycloadditions of nitrones to (*E*)-α,β-unsaturated esters.[10,15c,23] Now, concerning the major *endo* cycloadducts, the important facts in relation to the *syn*/*anti* selectivity are the following:

(i) For the non hydroxylic olefins **5** and **6** (Table 1, entries 2, 3, 8, and 9) the *anti* approach clearly predominates, in agreement with the *inside alkoxy* theory (Scheme 1).

(ii) For alcohol **8** (Table 1, entries 5 and 11) a preference for the *syn* approach is observed, also according with the *outside alcohol* model.

(iii) On the contrary, in the cycloadditions to the allylic alcohols **3** and **4** (Table 1, entries 1, 6, and 7) the *anti* isomers again clearly predominate. We therefore conclude that the aromatic ring is not the cause for the unexpected selectivity. The hypothesis that the formation of an intramolecular hydrogen bond between the alkoxy group and the allylic alcohol in the dipolarophile competes advantageously with the intermolecular hydrogen bond with the oxygen atom of the dipole seems more plausible. Consequently, alcohols **3** and **4** would in practice behave as ethers in the cycloaddition process.

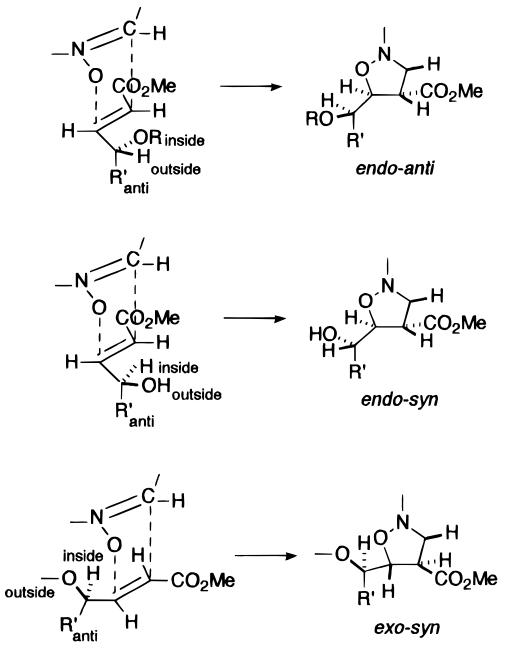
(iv) On the other hand, the typical alcohol selectivity shown by diol **7** (Table 1, entries 4 and 10) can be attributed to the fact that this olefin is able simultaneously to form intra- and intermolecular hydrogen bonds in the transition state.

These results indicate that the Houk transition-state model can be extended to *endo* adducts of 1,2-disubstituted electron-poor substrates, but the possibility of intramolecular hydrogen bonding must be taken into account. Considering this, we can now explain some results previously reported by others. For instance, Kanemasa *et al.*[3e] found the cycloaddition of nitrile oxide to methyl 2-(1-hydroxyalkyl)propenoates to be *anti* selective and, although the authors indicate this result is opposite to the one expected, they did not give any explanation. Also, in the recent work by Annunziata *et al.*,[3f] dealing with analogous cycloadditions, identical selectivity was obtained using ether derivatives or alcohols, but no comments were made about this result or about hydrogen bonds. All those allylic alcohols are substrates capable of forming an intramolecular hydrogen bond which would explain their behaviour as ether derivatives.

For the minor *exo* adducts we observed that the *syn* isomers predominate over the *anti* in all the cases studied. This fact is in agreement with a model in which the most favorable transition state should have the bulky alkyl chain in *anti* position and the smallest group (proton) occupying the most steric demanding *inside* position, which lies directly above or below the nitrone skeleton (Scheme 1).

In conclusion, our studies indicate that the Houk transition-state model may be extended to adducts derived from an *endo* transition state when using 1,2-disubstituted electron-poor olefins, but for allylic alcohols, the possibility of intramolecular hydrogen bonding can not be neglected. Adducts derived from an *exo* transition state present always *syn* selectivity.

Scheme 1



Experimental Section

General Procedures. See ref 16. CH_2Cl_2 free of ethanol and stabilized with amylene was used in the mesylation reactions. GC analyses were performed with a capillary column (crosslinked methyl silicone gum, 12 m × 0.2 mm × 0.3 μm), $T_{inj} = 180$ °C, $T = 120$ °C. NMR spectra were recorded by Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona. Acetone-d_6 was used as solvent for NMR experiments unless otherwise stated. The following starting compounds were prepared according to previously described methods: **1**,[14] **2**,[15] **3**,[18] (*R*)-**3**,[18] **5**,[18], **6**,[19] **7**.[11a,20] The reactions between nitrone **1** and olefins **3** and **6**, and between nitrone **2** and alkene **3** have been already published.[10]

Methyl (*E*)-6-Methoxy-2-hexenoate. 4-Methoxybutanol (8.02 g, 76.9 mmol) was oxidized with PCC following literature data.[26] To the concentrated solution (200 mL) containing the crude 4-methoxybutanal (without distillation) (methoxycarbonyl)methylenetriphenylphosphorane (20.58 g, 61.5 mmol) was added in small portions. After 2 h at rt the solvent was removed and the solid residue was washed several times with a hot mixture of ether−hexane (1:1). The solvent of the combined extracts was removed and the crude material (7.10 g) was purified by flash chromatography using ether−hexane (3:1) as eluent to yield pure methyl 6-methoxy-2-hexenoate as a colorless liquid (4.80 g, 30.4 mmol, 39% overall yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.94 (dt, J = 15.7, 6.9 Hz, 1 H), 5.80 (dt, J = 15.7, 1.8 Hz, 1 H), 3.69 (s, 3H), 3.35 (t, J = 6.4 Hz, 2 H), 3.28 (s, 3 H), 2.25 (q, J = 8.0 Hz, 2 H), 1.69 (quintuplet, J = 6.6 Hz, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.4, 148.3, 120.8, 71.1, 58.0, 50.8, 28.3, 27.6.

Methyl (*E*)-4-Hydroxy-6-methoxy-2-hexenoate (4). Selenium dioxide (1.37 g, 12.3 mmol) was added to a solution of methyl (*E*)-6-methoxy-2-hexenoate (1.50 g, 9.5 mmol) in dioxane (150 mL), and the mixture was kept at reflux for 6 h. The cold solution was filtered, and the solvent was removed to afford 1.82 g of a yellow oil. Flash chromatography of this crude material afforded the following fractions: (i) 210 mg (1.3 mmol) of starting product using hexane-ethyl acetate (3:1) as eluent; (ii) 480 mg (2.8 mmol, 34% yield) of methyl (*E*)-6-methoxy-4-oxo-2-hexenoate as a pale yellow solid using the same eluent; and (iii) 810 mg (4.7 mmol, 57% yield) of methyl

(26) Stetter, H.; Leinen, H. T. *Chem. Ber.* **1983**, *116*, 254.

(*E*)-4-hydroxy-6-methoxy-2-hexenoate (**4**) as a pale yellow oil using hexane−ethyl acetate (1:1) as eluent. Methyl 6-methoxy-4-oxo-2-hexenoate: mp 35−7 °C (ether/hexane); IR (KBr) 1731, 1699, 1636 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.05 (d, J = 16.1 Hz, 1 H), 6.65 (d, J = 16.1 Hz, 1 H), 3.77 (s, 3 H), 3.66 (t, J = 6.2 Hz, 2 H), 3.29 (s, 3 H), 2.85 (t, J = 6.2 Hz, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 197.6, 165.6, 139.3, 130.4, 66.9, 58.6, 52.1, 41.2; MS *m*/*z* 141 (4), 113 (100). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.03. Found: C, 55.85; H, 7.06. **4**: IR (KBr) 3444, 1727, 1660 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.90 (dd, J = 16.1, 4.4 Hz, 1 H), 6.07 (dd, J = 16.1, 1.8 Hz, 1 H), 4.45 (m, 1 H), 3.69 (s, 3 H), 3.57 (ddd, J = 9.5, 6.6, 4.4 Hz, 1 H), 3.54 (ddd, J = 9.5, 6.6, 3.7 Hz, 1 H), 3.30 (s, 3 H), 1.86 (m, 1 H), 1.72 (m, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.7, 150.0, 119.3, 69.8, 69.1, 58.4, 51.1, 35.2; MS *m*/*z* 175 (0.2), 143 (5), 115 (37), 45 (100). Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.96; H, 8.14.

Methyl (*E*)-4-Hydroxy-2-pentenoate (8). A magnetically stirred solution of methyl (*E*)-4-oxo-2-pentenoate[22] (2.67 g, 20.8 mmol) in anhydrous methanol (75 mL) under argon was cooled to 0 °C. $NaBH_4$ was slowly added and after 50 min at the same temperature the solvent was removed. $CHCl_3$ (20 mL) and 1 M sulfuric acid (20 mL) were added to the residue. The organic phase was washed with $CHCl_3$ (2 × 20 mL), dried over anhydrous Na_2SO_4, and the solvent was removed to afford 2.60 g of crude material. Purification by flash chromatography using hexane−ethyl acetate (1:1) as eluent yielded compound **4** as a colorless oil (2.49 g, 19.2 mmol, 92% yield), whose spectroscopic data matched with those previously published.[21]

Reaction between Nitrone 1 and Olefin (*R*)-3. The reaction was run under the same conditions previously described for racemic **3**.[10] (2*S*,3*S*,3a*R*,1′*R*)-**9a**: $[\alpha]^{20}_D = 83°$ (c = 1.73 in $CHCl_3$). (2*R*,3*R*,3a*S*,1′*R*)-**9b**: $[\alpha]^{20}_D = -75°$ (c = 1.22 in $CHCl_3$).

Reaction between Nitrone 1 and Olefin 5. A solution of nitrone **1** (914 mg, 10.7 mmol) and mesylate **5** (1.40 g, 4.3 mmol) in $CHCl_3$ (20 mL) was heated at reflux for 48 h under argon. Removal of the solvent gave 2.60 g of crude material. Purification by flash chromatography using hexane−ethyl acetate (1:4) as eluent yielded the following fractions: (i) methyl (2*RS*,3*RS*,3a*SR*)-2-[(1*SR*)-3-(benzyloxy)-1-(mesyloxy)-propyl]hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (**10a**) (343 mg, 0.83 mmol, 19% yield) as a colorless oil; and (ii) 1.15 g (2.8 mmol, 65% yield) of a mixture of compounds **10a**, **10b**, and traces of the corresponding *exo* adducts.

Repeated flash chromatography of the second fraction under the same conditions gave 225 mg (0.54 mmol, 12% yield) of product **10a** and 902 mg (2.18 mmol, 51% yield) of a mixture of all four adducts. In the last fraction the ratio **10a**/**10b** was 1.6:1 and the *endo*/*exo* was 10:1. The overall yield was 59% of **10a** and 18% of **10b**. For spectroscopic data for **10a** and **10b** see below.

Reaction between Nitrone 1 and Olefin 7. A solution of nitrone **1** (262 mg, 3.1 mmol) and methyl (*E*)-4,6-dihydroxy-2-pentenoate (**7**, 300 mg, 2.05 mmol) in $CHCl_3$ (10 mL) was heated at reflux for 1 d under argon. Removal of the solvent gave 570 mg of crude material. Purification by flash chromatography on silica gel (J. T. Baker 30−60 μm) using ether−methanol (30:1) as eluent yielded the following fractions: (i) methyl (2*RS*,3*RS*,3a*SR*)-2-[(1*SR*)-1,2-dihydroxyethyl]hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (**12a**) (167 mg, 0.72 mmol, 34% yield) as a colorless oil; and (ii) 235 mg (1.02 mmol, 49% yield) of the *endo-syn* isomer, **12b**. **12a**: IR (film) 3378, 1736 cm^{-1}; ^1H-NMR (400 MHz) δ 4.36 (t, J = 6.1 Hz, 1 H), 3.81 (q, $J \approx$ 7.6 Hz, 1 H), 3.76 (dd, J = 8.2, 6.1 Hz, 1 H), 3.68 (m, 1 H), 3.67 (s, 3 H), 3.61 (dd, J = 11.0, 4.0 Hz, 1 H), 3.49 (dd, J = 11.0, 5.5 Hz, 1 H), 3.20 (ddd, J = 13.1, 7.9, 4.5 Hz, 1 H), 2.97 (dt, J = 13.1, 7.9 Hz, 1 H), 1.95 (m, 1 H), 1.79−1.65 (m, 2 H), 1.63−1.55 (m, 1 H); ^{13}C-NMR (100 MHz) δ 172.4, 79.5, 73.6, 68.9, 64.1, 56.3, 54.2, 52.0, 27.2, 24.6; MS *m*/*z* 231 (12), 200 (5), 86 (100). Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.92; H, 7.40; N, 6.14. **12b**: IR (film) 3378, 1735 cm^{-1}; ^1H-NMR (400 MHz) δ 4.42 (dd, J = 6.7, 3.4 Hz, 1 H), 3.85 (q, $J \approx$ 7.5 Hz, 1 H), 3.81 (t, J = 7.6, 1 H), 3.69 (s, 3 H), 3.61−3.48 (m, 3 H), 3.20 (ddd, J = 13.1, 7.6, 4.7 Hz, 1 H), 2.99 (dt, J = 13.1, 7.9 Hz, 1 H), 1.95 (m, 1 H), 1.83−1.69 (m, 2 H), 1.55 (m, 1 H); ^{13}C-NMR (62.5 MHz) δ 171.8, 78.9, 73.1, 68.3, 64.3, 56.8, 53.3, 52.1, 27.6, 24.7; MS *m*/*z* 231 (7), 200 (11), 86 (100). Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 52.07; H, 7.39; N, 6.18.

Reaction between Nitrone 1 and Olefin 8. A solution of nitrone **1** (1.69 g, 19.9 mmol) and methyl (*E*)-4-hydroxy-2-pentenoate (**8**) (800 mg, 6.15 mmol) in $CHCl_3$ (45 mL) was heated at reflux for 40 h under argon. Flash chromatography of the crude material (1.74 g) using ethyl acetate as eluent yielded two fractions. The GC−MS analysis of the less polar fraction (437 mg, 2.03 mmol, 33% yield), a colorless oil, revealed the presence of three compounds: t_1 = 10.0 min (81%), t_2 = 10.9 min (10%), t_3 = 11.2 min (4%). The major product was methyl (2*RS*,3*RS*,3a*SR*)-2-[(1*SR*)-1-hydroxyethyl]hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (**13a**), and the minor components were the *exo-anti*, **13c**, and *exo-syn*, **13d**, adducts. The second fraction, a colorless oil, was identified as methyl (2*RS*,3*RS*,3a*SR*)-2-[(1*RS*)-1-hydroxyethyl]hexahydropyrrolo-[1,2-*b*]isoxazole-3-carboxylate (**13b**, 745 mg, 3.47 mmol, 57% yield). **13a** (81% stereochemical purity): IR (film) 3213, 1731 cm^{-1}; ^1H NMR (400 MHz) δ 4.15 (t, $J \approx$ 5.7 Hz, 1 H), 3.81 (m, 1 H), 3.80 (q, $J \approx$ 7.7 Hz, 1 H), 3.69 (dd, J = 8.0, 6.0 Hz, 1 H), 3.68 (s, 3 H), 3.20 (ddd, J = 13.0, 8.0, 4.4 Hz, 1 H), 2.95 (dt, J = 13.0, 7.8 Hz, 1 H), 1.95 (m, 1 H), 1.80−1.63 (m, 2 H), 1.57 (m, 1 H), 1.07 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz) δ 170.8, 83.1, 69.1, 69.0, 56.3, 53.3, 52.1, 27.2, 24.5, 19.8; MS *m*/*z* 215 (13), 85 (100). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H: 7.96; N, 6.51. Found: C, 55.74; H, 8.03; N, 6.44. **13b**: IR (film) 3220, 1732 cm^{-1}; ^1H NMR (400 MHz) δ 4.09 (dd, J = 7.1, 4.7 Hz, 1 H), 3.78 (q, $J \approx$ 7.8 Hz, 1 H), 3.67 (m, 1 H), 3.65 (s, 3 H), 3.58 (t, $J \approx$ 7.5 Hz, 1 H), 3.17 (ddd, J = 13.0, 7.7, 4.7 Hz, 1 H), 2.95 (dt, J = 13.0, 7.7 Hz, 1 H), 1.93 (m, 1 H), 1.75 (m, 1 H), 1.65 (m, 1 H), 1.53 (m, 1 H), 1.07 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz) δ 171.9, 82.6, 68.7, 68.2, 56.7, 53.7, 52.1, 27.5, 24.6, 19.6. MS *m*/*z* 215 (22), 86 (100). Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.80; H, 8.05; N, 6.61.

Reaction between Nitrone 2 and Olefin (*R*)-3. The reaction was run under the same conditions described for racemic **3**.[10] (2*S*,3*S*,3a*R*,1′*R*)-**14a**: $[\alpha]^{20}_D = -29°$ (c = 2.30 in $CHCl_3$). (2*R*,3*R*,3a*S*,1′*R*)-**14b**: $[\alpha]^{20}_D = 10.5°$ (c = 2.50 in $CHCl_3$). (2*R*,3*R*,3a*R*,1′*R*)-**14d**: $[\alpha]^{20}_D = -51°$ (c = 3.4 in $CHCl_3$).

Reaction between Nitrone 2 and Olefin 4. To a solution of nitrone **2** (prepared from 1.13 g (11.2 mmol) of *N*-hydroxypiperidine and 7.30 g (33.6 mmol) of yellow HgO) in CH_2Cl_2 (25 mL) was added a solution of methyl (*E*)-6-methoxy-4-hydroxy-2-hexenoate (**4**) (1.38 g, 7.9 mmol) in CH_2Cl_2 (2 mL), and the mixture was kept at rt for 2 d under nitrogen. Flash chromatography of the crude material (2.56 g) using ether as eluent afforded the following fractions: (i) 231 mg (0.85 mmol, 11% yield) of a 7:1 mixture of methyl (2*RS*,3*RS*,3a*RS*)-2-[(1*RS*)-1-hydroxy-3-methoxypropyl]hexahydro-2*H*-isoxazolo-[2,3-*a*]pyridine-3-carboxylate (**15d**) and the *exo-anti* isomer, **15c**, as an oil, from which **15d** crystallized (ethyl acetate/pentane); (ii) 960 mg (3.51 mmol, 44% yield) of the *endo-anti* isomer, **15a**, as a colorless oil; and (iii) 500 mg (1.85 mmol, 23% yield) of the *endo-syn* isomer, **15b**, as a colorless oil. **15a**: IR (film) 3454, 1738 cm^{-1}; ^1H-NMR (400 MHz) δ 4.18 (t, J = 5.0 Hz, 1 H), 4.07 (d, J = 5.0 Hz, 1 H), 3.73 (dtd, J = 9.7, 5.0, 3.2 Hz, 1 H), 3.64 (s, 3 H), 3.52−3.40 (m, 2 H), 3.27 (m, 1 H), 3.24 (dd, J = 8.3, 5.0 Hz, 1 H), 3.23 (s, 3 H), 2.36 (ddd, J = 10.9, 8.3, 2.5 Hz, 1 H), 2.30 (ddd, J = 12.4, 9.1, 3.0 Hz, 1 H), 1.87 (m, 1 H), 1.75−1.65 (m, 3 H), 1.52−1.40 (m, 2 H), 1.25−1.10 (m, 2 H); ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 171.9, 81.6, 70.0, 69.3, 69.2, 58.5, 55.2, 51.5, 50.9, 32.5, 26.4, 24.0, 23.3; MS *m*/*z* 273 (15), 100 (91), 99 (89), 84 (100). Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H: 8.48; N, 5.12. Found: C, 57.19; H, 8.51; N, 5.10. **15b**: IR (film) 3452, 1738 cm^{-1}; ^1H-NMR (400 MHz) δ 4.28 (dd, J = 5.2, 4.0 Hz, 1 H), 3.83 (d, J = 7.1 Hz, 1 H), 3.70 (ddt, J = 9.4, 7.1, 3.8 Hz, 1 H), 3.64 (s, 3 H), 3.52−3.40 (m, 2 H), 3.28 (m, 1 H), 3.24 (s, 3 H), 3.22 (dd, J = 8.4, 5.2 Hz, 1 H), 2.37 (ddd, J = 11.7, 8.4, 2.7 Hz, 1 H), 2.32 (ddd, J = 12.4, 9.2, 3.0 Hz, 1 H), 1.87 (dq, J = 9.2, 2.5 Hz, 1 H), 1.77−1.55 (m, 4 H), 1.45 (m, 1 H), 1.25−1.10 (m, 2 H); ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 171.9, 81.2, 70.0, 69.9, 69.4, 58.6, 55.3,

52.3, 51.7, 33.4, 26.5, 24.2, 23.4; MS *m*/*z* 273 (10), 100 (100), 99 (48), 84 (74). Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 56.97; H, 8.60; N, 5.12. **15d**: mp: 51−2 °C (ethyl acetate/pentane); IR (KBr) 3462, 1738 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 4.11 (t, $J \approx 4.4$ Hz, 1 H), 3.72 (m, 1 H), 3.69 (s, 3 H), 3.56−3.45 (m, 2 H), 3.39 (m, 1 H), 3.31 (s, 3 H), 3.12 (dd, $J = 10.2$, 5.1 Hz, 1 H), 2.48−2.36 (m, 2 H), 2.07 (br d, $J = 12.4$ Hz, 1 H), 1.90−1.65 (m, 4 H), 1.65−1.20 (m, 3 H); ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 172.2, 81.1, 71.6, 70.4, 69.6, 58.7, 54.9, 54.3, 52.2, 33.8, 28.6, 24.4, 23.2; MS *m*/*z* 273 (11), 100 (100), 84 (65). Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.30; H, 8.50; N, 5.16.

Reaction between Nitrone 2 and Olefin 5. To a solution of nitrone **2** (prepared from 108 mg (1.07 mmol) of *N*-hydroxypiperidine and 693 mg (3.21 mmol) of yellow HgO) in CH_2Cl_2 (5 mL) was added methyl (*E*)-6-(benzyloxy)-4-(mesyloxy)-2-hexenoate (**5**) (351 mg, 1.07 mmol), and the mixture was kept at rt for 4 d under nitrogen. Flash chromatography of the crude material using hexane−ethyl acetate (1:2) as eluent afforded the following fractions: (i) 95 mg (0.21 mmol, 20% yield) of a 2:3 mixture of methyl (2*RS*,3*RS*,3a*RS*)-2-[(1*SR*)-3-(benzyloxy)-1-(mesyloxy)propyl]hexahydro-2*H*-isoxazolo[2,3-*a*]-pyridine-3-carboxylate (**16c**) and the *exo-syn* isomer, **16d**, respectively; and (ii) 310 mg (0.72 mmol, 68% yield) of a 2.4:1 mixture of the *endo-anti*, **16a**, and *endo-syn*, **16b**, adducts, respectively. For spectroscopic data for **16a**−**16d** see below.

Reaction between Nitrone 2 and Olefin 6. To a solution of nitrone **2** (prepared from 1.09 g (10.8 mmol) of *N*-hydroxypiperidine and 6.30 g (29.2 mmol) of yellow HgO) in CH_2Cl_2 (50 mL) was added methyl (*S*,*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenoate (**6**) (1.00 g, 5.4 mmol), and the mixture was kept at rt for 20 h under nitrogen. Flash chromatography of the crude product using hexane−ether mixtures of increasing polarity afforded the following fractions: (i) 77 mg (0.27 mmol, 5% yield) of methyl (2*S*,3*S*,3a*S*)-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate (**17c**) as a colorless oil; (ii) 185 mg (0.65 mmol, 12% yield) of the (2*R*,3*R*,3a*R*,4′*R*)-isomer, **17d**, as a colorless oil; (iii) 769 mg (2.70 mmol, 50% yield) of the (2*S*,3*S*,3a*R*,4′*R*)-isomer, **17a**, as a colorless oil; and (iv) 400 mg (1.40 mmol, 26% yield) of the (2*R*,3*R*,3a*S*,4′*R*)-isomer, **17b**, as a solid. **17a**: IR (film) 1741 cm^{-1}; ^{1}H NMR (400 MHz, 250 K) δ 4.29 (dd, $J = 6.8$, 4.9 Hz, 1 H), 4.07 (td, $J = 6.4$, 4.6 Hz, 1 H), 4.03 (dd, $J = 8.2$, 6.3 Hz, 1 H), 3.68 (dd, $J = 8.2$, 4.6 Hz, 1 H), 3.64 (s, 3 H), 3.27 (br dt, $J = 9.2$, 3.0 Hz, 1 H), 3.21 (dd, $J = 8.2$, 4.9 Hz, 1 H), 2.42 (ddd, $J = 11.0$, 8.2, 2.3 Hz, 1 H), 2.28 (ddd, $J = 12.2$, 9.2, 3.0 Hz, 1 H), 1.90 (m, 1 H), 1.72−1.62 (m, 2 H), 1.44 (m, 1 H), 1.28 (s, 3 H), 1.23 (s, 3 H), 1.15−1.03 (m, 2 H); ^{13}C NMR (100 MHz, 250 K) δ 172.2, 109.5, 79.4, 76.2, 69.4, 67.1, 55.3, 52.9, 51.8, 27.3, 26.6, 25.1, 24.8, 23.9; MS *m*/*z* 285 (16), 270 (28), 100 (93), 99 (70), 84 (100); $[\alpha]^{20}_D = -39.4°$ ($c = 2.33$ in $CHCl_3$). Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.87; H, 8.23; N, 4.93. **17b**: mp 44−5 °C; IR (KBr) 1740 cm^{-1}; ^{1}H NMR (400 MHz, 250 K) δ 4.37 (t, $J = 5.2$ Hz, 1 H), 4.24 (ddd, $J = 7.2$, 6.1, 5.2 Hz, 1 H), 4.03 (dd, $J = 8.5$, 7.2 Hz, 1 H), 3.71 (dd, $J = 8.5$, 6.1 Hz, 1 H), 3.64 (s, 3 H), 3.30 (br dt, $J = 9.2$, 2.8 Hz, 1 H), 3.16 (dd, $J = 8.5$, 5.2 Hz, 1 H), 2.40 (ddd, $J = 11.2$, 8.5, 2.4 Hz, 1 H), 2.31 (ddd, $J = 12.3$, 9.2, 3.0 Hz, 1 H), 1.88 (m, 1 H), 1.72−1.62 (m, 2 H), 1.45 (m, 1 H), 1.31 (s, 3 H), 1.24 (s, 3 H), 1.30−1.05 (m, 2 H); ^{13}C NMR (100 MHz, 250 K) δ 172.1, 109.7, 79.1, 75.8, 69.9, 65.7, 55.5, 52.1, 51.8, 27.4, 26.4, 25.1, 24.8, 24.0; MS *m*/*z* 285 (17), 270 (34), 100 (100), 99 (76), 84 (99); $[\alpha]^{20}_D = 23.6°$ ($c = 1.44$ in $CHCl_3$). Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.89; H, 8.16; N, 4.86. **17c**: IR (film) 1741 cm^{-1}; ^{1}H NMR (400 MHz, 250 K) δ 4.09 (dd, $J = 7.9$, 5.2 Hz, 1 H), 4.01 (m, 2 H), 3.88 (m, 1 H), 3.67 (s, 3 H), 3.24 (dt, $J = 9.2$, 3.0 Hz, 1 H), 2.94 (dd, $J = 10.1$, 5.2 Hz, 1 H), 2.35 (ddd, $J = 12.2$, 9.2, 3.0 Hz, 1 H), 2.25 (ddd, $J = 11.0$, 10.1, 2.4 Hz, 1 H), 2.01 (m, 1 H), 1.72 (m, 1 H), 1.67 (m, 1 H), 1.48 (m, 1 H), 1.40 (m, 1 H), 1.24 (s, 3 H), 1.20 (s, 3 H), 1.19 (m, 1 H); ^{13}C NMR (100 MHz, 250 K) δ 172.5, 109.5, 79.3, 77.8, 71.8, 67.6, 56.7, 55.5, 52.2, 29.8, 27.1, 25.4, 25.0, 23.8. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.90; H, 8.20; N, 4.92. **17d**: IR (film) 1739 cm^{-1}; ^{1}H NMR (400 MHz, 250 K) δ 4.26 (dt, $J = 7.5$, 6.5 Hz, 1 H), 4.16 (dd, $J = 7.5$, 5.6 Hz, 1 H), 4.02 (dd, $J = 8.5$, 6.7 Hz, 1 H), 3.80 (dd, $J = 8.5$, 6.1 Hz, 1 H), 3.68 (s, 3 H), 3.27 (dt, $J = 9.2$, 3.4 Hz, 1 H), 2.82 (dd, $J = 9.9$, 5.6 Hz, 1 H), 2.37 (ddd, $J = 12.2$, 9.2, 2.9 Hz, 1 H), 2.28 (ddd, $J = 11.1$, 9.9, 2.5 Hz, 1 H), 2.00 (m, 1 H), 1.74 (m, 1 H), 1.68 (m, 1 H), 1.49 (m, 1 H), 1.34 (m, 1 H), 1.30 (s, 3 H), 1.23 (s, 3 H), 1.17 (m, 1 H); ^{13}C NMR (100 MHz, 250 K) δ 172.3, 109.7, 80.1, 77.1, 71.0, 65.4, 55.3, 54.5, 52.4, 29.0, 26.5, 25.0, 24.9, 23.7; MS *m*/*z* 285 (23), 270 (42), 100 (100), 99 (93), 84 (98); $[\alpha]^{20}_D = -25.4°$ ($c = 1.05$ in $CHCl_3$). Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.99; H, 8.32; N, 4.96.

Reaction between Nitrone 2 and Olefin 7. To a solution of nitrone **2** (prepared from 630 mg (6.23 mmol) of *N*-hydroxypiperidine and 4.05 g (18.7 mmol) of yellow HgO) in CH_2Cl_2 (15 mL) was added a solution of methyl (*E*)-4,6-dihydroxy-2-pentenoate (**7**) (700 mg, 4.79 mmol) in CH_2Cl_2 (2 mL), and the mixture was kept at rt for 3 d under nitrogen. Flash chromatography of the crude material (1.34 g) on silica gel (J. T. Baker 30−60 μm) using ether−methanol (30:1) as eluent afforded the following fractions: (i) 110 mg (0.75 mmol) of starting olefin **7**; (ii) 170 mg (0.69 mmol, 17% yield) of a 1:3 mixture of methyl (2*RS*,3*RS*,3a*RS*)-2-[(1*SR*)-1,2-dihydroxyethyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate (**18c**) and the *exo-syn* isomer, **18d**, respectively, as a colorless oil; (iii) 350 mg (1.43 mmol, 35% yield) of the *endo-anti* isomer, **18a**, as a colorless oil; and (iv) 420 mg (1.71 mmol, 42% yield) of the *endo-syn* isomer, **18b**, as a colorless oil. **18a**: IR (film) 3398, 1737 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.33 (t, $J = 5.0$ Hz, 1 H), 3.72 (m, 1 H), 3.69 (s, 3 H), 3.63 (m, 1 H), 3.51 (dd, $J = 11.5$, 6.0 Hz, 1 H), 3.42 (m, 1 H), 3.31 (dd, $J = 8.2$, 5.0 Hz, 1 H), 2.38−2.30 (m, 2 H), 1.90 (br d, $J = 10.5$ Hz, 1 H), 1.75−1.60 (m, 2 H), 1.50 (m, 1 H), 1.40−1.10 (m, 2 H); ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 172.3, 79.4, 71.5, 69.2, 63.5, 55.3, 51.8, 51.7, 26.5, 24.2, 23.4; MS *m*/*z* 245 (9), 100 (62), 99 (100). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.73; H, 7.82; N, 5.68. **18b**: IR (film) 3390, 1736 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 4.41 (dd, $J = 5.1$, 2.2 Hz, 1 H), 3.65 (s, 3 H), 3.70−3.35 (m, 4 H), 3.30 (dd, $J = 8.5$, 5.1 Hz, 1 H), 2.39−2.32 (m, 2 H), 1.88 (br d, $J = 8.8$ Hz, 1 H), 1.75−1.45 (m, 3 H), 1.40−1.10 (m, 2 H); ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 172.0, 79.6, 71.6, 69.3, 64.2, 55.3, 52.3, 51.8, 26.5, 24.2, 23.4; MS *m*/*z* 245 (8), 99 (100). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.82; H, 7.88; N, 5.70. **18c** (observable signals from the mixture **18c**/**18d** 1:3): ^{1}H-NMR (250 MHz, $CDCl_3$) δ 4.34 (dd, $J = 5.3$, 4.0 Hz, 1 H), 3.89 (m, 1 H), 3.20 (dd, $J = 9.9$, 5.3 Hz, 1 H); ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 79.4, 73.7, 69.9, 62.6, 54.8, 52.6, 28.6. **18d** (from the mixture **18c**/**18d** 1:3): ^{1}H-NMR (250 MHz, $CDCl_3$) (85% *trans*-invertomer) δ 4.29 (dd, $J = 5.3$, 2.7 Hz, 1 H), 3.72 (s, 3 H), 3.80−3.60 (m, 3 H), 3.39 (m, 1 H), 3.21 (dd, $J = 9.8$, 5.3 Hz, 1 H), 2.49−2.39 (m, 2 H), 2.12 (m, 1 H), 1.85−1.75 (m, 2 H), 1.61−1.20 (m, 3 H); ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 171.9, 78.4, 74.2, 70.0, 64.2, 54.9, 54.0, 52.3, 28.5, 24.4, 23.1. Mixture **18c**/**18d** 1:3: IR (film) 3397, 1737 cm^{-1}; MS *m*/*z* 245 (10), 100 (100), 99 (83). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.80; H, 7.85; N, 5.73.

Reaction between Nitrone 2 and Olefin 8. To a solution of nitrone **2** (prepared from 931 mg (9.22 mmol) of *N*-hydroxypiperidine and 5.97 g (27.7 mmol) of yellow HgO) in CH_2Cl_2 (50 mL) was added methyl (*E*)-4-hydroxy-2-pentenoate (**8**) (800 mg, 6.15 mmol), and the mixture was kept at rt for 20 h under nitrogen. Flash chromatography of the crude product using hexane−ether mixtures of increasing polarity afforded the following fractions: (i) 70 mg (0.30 mmol, 5% yield) of methyl (2*RS*,3*RS*,3a*RS*)-2-[(1*SR*)-1-hydroxyethyl]-hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate (**19c**) as a colorless oil; (ii) 267 mg (1.17 mmol, 19% yield) of the (2*RS*,3*RS*,3a*RS*,1′*RS*)-isomer, **19d**, as a colorless oil; (iii) 465 mg (2.03 mmol, 33% yield) of the (2*RS*,3*RS*,3a*SR*,1′*SR*)-isomer, **19a**, as a solid; and (iv) 521 mg (2.28 mmol, 37% yield) of the (2*RS*,3*RS*,3a*SR*,1′*RS*)-isomer, **19b**, as a solid. **19a**: mp 54−5 °C; IR (film) 3409, 1739 cm^{-1}; ^{1}H NMR (400 MHz, 250 K) δ 4.24 (d, $J = 4.6$ Hz, 1 H), 4.11 (t, $J = 5.0$ Hz, 1 H), 3.72 (m, 1 H), 3.63 (s, 3 H), 3.25 (m, 1 H), 3.22 (dd, $J = 8.4$, 5.0 Hz, 1 H), 2.35 (ddd, $J = 10.6$, 8.4, 2.5 Hz, 1 H), 2.28 (ddd, $J = 12.3$, 9.2, 3.0 Hz, 1 H), 1.85 (m, 1 H), 1.70−1.60 (m, 2 H), 1.42 (m, 1 H), 1.23−1.05 (m, 2 H), 1.05 (d, $J = 6.6$ Hz, 3 H); ^{13}C NMR (100

MHz, 250 K) δ 172.7, 83.5, 69.6, 66.9, 55.4, 51.8, 51.6, 27.2, 24.8, 24.0, 20.1; MS *m*/*z* 229 (25), 100 (51), 99 (100). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.06; H, 8.33; N, 5.87. **19b**: mp 51−2 °C; IR (film) 3440, 1738 cm^{-1}; ^1H NMR (400 MHz, 250 K) (*ca*. 95% *trans*-invertomer) δ 4.20 (t, J = 5.1 Hz, 1 H), 4.18 (d, J = 6.4 Hz, 1 H), 3.74 (m, 1 H), 3.61 (s, 3 H), 3.25 (m, 1 H), 3.16 (dd, J = 8.4, 5.1 Hz, 1 H), 2.35 (ddd, J = 11.3, 8.4, 2.4 Hz, 1 H), 2.28 (ddd, J = 12.2, 9.1, 2.9 Hz, 1 H), 1.85 (m, 1 H), 1.72−1.55 (m, 2 H), 1.42 (m, 1 H), 1.30−1.10 (m, 2 H), 1.07 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, 250 K) δ 172.4, 82.6, 69.7, 67.0, 55.4, 52.1, 51.7, 27.2, 24.7, 24.0, 19.3; MS *m*/*z* 229 (24), 100 (76), 99 (100). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.70; H, 8.30; N, 6.14. **19c**: ^1H NMR (400 MHz, 250 K) (*ca*. 95% *trans*-invertomer) δ 4.06 (br s, 1 H), 3.93 (dd, J = 6.4, 5.2 Hz, 1 H), 3.76 (m, 1 H), 3.65 (s, 3 H), 3.27 (m, 1 H), 3.08 (dd, J = 10.1, 5.2 Hz, 1 H), 2.34 (ddd, J = 12.2, 9.0, 2.9 Hz, 1 H), 2.28 (ddd, J = 11.3, 10.1, 2.6 Hz, 1 H), 2.02 (m, 1 H), 1.75−1.60 (m, 2 H), 1.49 (m, 1 H), 1.35−1.10 (m, 2 H), 1.08 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, 250 K) δ 172.8, 82.9, 71.6, 69.6, 55.1, 54.5, 52.0, 28.8, 24.6, 23.5, 19.9; MS *m*/*z* 229 (1), 100 (100), 99 (99). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.79; H, 8.40; N, 6.10. **19d**: IR (film) 3450, 3424, 2941, 2858, 1739 cm^{-1}; ^1H NMR (400 MHz, 250 K) (*ca*. 95% *trans*-invertomer) δ 4.13 (br s, 1 H), 3.87 (dd, J = 6.9, 5.5 Hz, 1 H), 3.70 (m, 1 H), 3.66 (s, 3 H), 3.30 (m, 1 H), 2.83 (dd, J = 9.9, 5.5 Hz, 1 H), 2.38−2.28 (m, 2 H), 2.00 (m, 1 H), 1.77−1.60 (m, 2 H), 1.48 (m, 1 H), 1.32 (m, 1 H), 1.16 (m, 1 H), 1.02 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, 250 K) δ 172.5, 83.7, 71.4, 69.1, 55.2, 54.9, 52.3, 28.9, 24.7, 23.7, 18.4; MS *m*/*z* 229 (16), 100 (99), 99 (100). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.86; H, 8.46; N, 6.11.

Methyl (2*RS*,3*RS*,3a*SR*)-2-[(1*SR*)-3-(Benzyloxy)-1-(mesyloxy)propyl]hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (10a). A solution of alcohol **9a** (74 mg, 0.22 mmol) in CH_2Cl_2 (6 mL) was added to a solution of mesyl chloride (86 μL, 1.1 mmol) in anhydrous pyridine (0.50 mL) at rt under argon. After 80 h at the same temperature, water (2 mL) was added, and the mixture was stirred during 2 h. The organic phase was washed with water (3 × 2 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed at 0.2 Torr. Flash chromatography of the crude material using ethyl acetate as eluent afforded 77 mg (0.19 mmol, 85% yield) of **10a** as a colorless oil. **10a**: ^1H NMR (400 MHz) δ 7.32 (m, 5 H), 4.97 (dt, J = 8.8, 3.8 Hz, 1 H), 4.54 (dd, J = 7.3, 3.8 Hz, 1 H), 4.52 (d, J = 11.6 Hz, 1 H), 4.46 (d, J = 11.6 Hz, 1 H), 3.88 (q, $J \approx$ 7.6 Hz, 1 H), 3.81 (t, $J \approx$ 7.5 Hz, 1 H), 3.72 (s, 3 H), 3.57 (m, 2 H), 3.23 (ddd, J = 13.1, 7.7, 4.1 Hz, 1 H), 3.17 (s, 3 H), 2.97 (dt, J = 13.1, 7.7 Hz, 1 H), 2.08−1.91 (m, 2 H), 1.90−1.67 (m, 3 H), 1.54 (m, 1 H); ^{13}C NMR (100 MHz) δ 171.6, 139.6, 128.9, 128.4, 128.1, 80.6, 79.6, 73.3, 68.9, 66.4, 56.8, 53.2, 52.4, 38.7, 32.2, 27.2, 24.5. Anal. Calcd for $C_{19}H_{27}NO_7S$: C, 55.19; H, 6.58; N, 3.39; S, 7.75. Found: C, 55.06; H, 6.66; N, 3.30; S, 7.66.

(2*S*,3*S*,3a*R*,1′*R*)-10a. The product was obtained in 82% yield starting with (2*S*,3*S*,3a*R*,1′*R*)-**9a**. (2*S*,3*S*,3a*R*,1′*R*)-**10a**: $[\alpha]^{20}_D = -20.0°$ (c = 0.90 in $CHCl_3$).

Methyl (2*RS*,3*RS*,3a*SR*)-2-[(1*RS*)-3-(Benzyloxy)-1-(mesyloxy)propyl]hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (10b). The same procedure described for the preparation of mesylate **10a** was used to prepare **10b** starting from alcohol **9b**. Compound **10b** was obtained as a colorless oil in 82% yield. **10b**: ^1H NMR (400 MHz) δ 7.33 (m, 5 H), 4.88 (br td, J = 7.8, 3.7 Hz, 1 H), 4.51 (d, J = 11.6 Hz, 1 H), 4.46 (t, $J \approx$ 7.0 Hz, 1 H), 4.45 (d, J = 11.6 Hz, 1 H), 3.85 (q, $J \approx$ 7.9 Hz, 1 H), 3.70 (s, 3 H), 3.68 (dd, J = 7.6, 6.1 Hz, 1 H), 3.60 (dd, J = 6.7, 5.5 Hz, 2 H), 3.21 (ddd, J = 13.4, 7.9, 4.0 Hz, 1 H), 3.12 (s, 3 H), 2.95 (dt, J = 13.4, 7.9 Hz, 1 H), 2.10−1.66 (m, 5 H), 1.54 (m, 1 H); ^{13}C NMR (100 MHz) δ 171.3, 139.5, 128.9, 128.4, 128.1, 80.2, 79.1, 73.3, 68.9, 66.2, 56.5, 54.0, 52.3, 38.3, 32.0, 27.5, 24.7. Anal. Calcd for $C_{19}H_{27}NO_7S$: C, 55.19; H, 6.58; N, 3.39; S, 7.75. Found: C, 55.18; H, 6.62; N, 3.33; S, 7.58.

(2*R*,3*R*,3a*S*,1′*R*)-10b. The product was obtained in 84% yield starting from (2*R*,3*R*,3a*S*,1′*R*)-**9b**. (2*R*,3*R*,3a*S*,1′*R*)-**10b**: $[\alpha]^{20}_D = 37°$ (c = 0.85 in $CHCl_3$).

Methyl (2*RS*,3*RS*,3a*SR*)-2-[(1*SR*)-3-(Benzyloxy)-1-(mesyloxy)propyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate (16a). The same procedure described for the preparation of mesylate **10a** was used to prepare **16a** starting from alcohol **14a**. Compound **16a** was obtained as a colorless oil in 95% yield after purification by flash chromatography using hexane−ethyl acetate (2:3) as eluent. **16a**: IR (film) 1738, 1359, 1196 cm^{-1}; ^1H NMR (400 MHz, 250 K) δ 7.36 (m, 5 H), 5.01 (ddd, J = 6.7, 4.3, 2.3 Hz, 1 H), 4.56 (dd, J = 5.2, 2.3 Hz, 1 H), 4.49 (d, J = 11.6 Hz, 1 H), 4.44 (d, J = 11.6 Hz, 1 H), 3.64 (s, 3 H), 3.56 (m, 2 H), 3.36 (m, 1 H), 3.30 (dd, J = 8.3, 5.2 Hz, 1 H), 3.18 (s, 3 H), 2.52 (ddd, J = 11.2, 8.3, 2.4 Hz, 1 H), 2.40 (ddd, J = 12.0, 9.1, 2.7 Hz, 1 H), 1.94−1.76 (m, 2 H), 1.74−1.61 (m, 2 H), 1.51−1.38 (m, 1 H), 1.29−1.16 (m, 2 H), 1.15−1.02 (m, 1 H); ^{13}C NMR (100 MHz, 250 K) δ 171.7, 139.2, 128.9, 128.4, 128.1, 79.9, 78.9, 73.0, 69.6, 65.8, 55.3, 52.0, 50.7, 38.7, 32.2, 27.4, 24.7, 23.7; MS *m*/*z* 427 (2), 100 (35), 99 (52), 91 (100), 84 (64). Anal. Calcd for $C_{20}H_{29}NO_7S$: C, 56.19; H, 6.84; N, 3.28; S, 7.50. Found: C, 56.13; H, 6.89; N, 3.28; S, 7.47.

(2*S*,3*S*,3a*R*,1′*R*)-16a. The product was obtained in 86% yield starting from (2*S*,3*S*,3a*R*,1′*R*)-**14a**. (2*S*,3*S*,3a*R*,1′*R*)-**16a**: $[\alpha]^{20}_D = -46°$ (c = 1.08 in $CHCl_3$).

Methyl (2*RS*,3*RS*,3a*SR*)-2-[(1*RS*)-3-(Benzyloxy)-1-(mesyloxy)propyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate (16b). The same procedure described for the preparation of mesylate **10a** was used to prepare **16b** starting from alcohol **14b**. Compound **16b** was obtained as a colorless solid in 84% yield after purification by flash chromatography using hexane−ethyl acetate (2:3) as eluent. **16b**: mp 87−8 °C (ethyl acetate−hexane); IR (film) 1737, 1357, 1198 cm^{-1}; ^1H NMR (400 MHz, 250 K) δ 7.36 (m, 5 H), 4.92 (q, J = 5.3 Hz, 1 H), 4.57 (t, J = 5.3 Hz, 1 H), 4.49 (d, J = 11.7 Hz, 1 H), 4.44 (d, J = 11.7 Hz, 1 H), 3.65 (s, 3 H), 3.57 (t, J = 6.0 Hz, 2 H), 3.33 (dd, J = 8.2, 5.3 Hz, 1 H), 3.31 (m, 1 H), 3.18 (s, 3 H), 2.47 (ddd, J = 11.3, 8.2, 2.4 Hz, 1 H), 2.35 (ddd, J = 12.1, 9.1, 2.7 Hz, 1 H), 1.98 (q, $J \approx$ 6.1 Hz, 2 H), 1.89 (br d, J = 12.2 Hz, 1 H), 1.73−1.61 (m, 2 H), 1.51−1.38 (m, 1 H), 1.27−1.04 (m, 2 H); ^{13}C NMR (100 MHz, 250 K) δ 171.8, 139.1, 128.9, 128.4, 128.1, 79.8, 79.0, 73.0, 69.5, 65.5, 55.4, 52.3, 52.0, 38.1, 32.0, 27.3, 24.7, 23.8; MS *m*/*z* 427 (1), 100 (30), 99 (37), 91 (100), 84 (96). Anal. Calcd for $C_{20}H_{29}NO_7S$: C, 56.19; H, 6.84; N, 3.28; S, 7.50. Found: C, 56.32; H, 6.99; N, 3.39; S, 7.55.

(2*R*,3*R*,3a*S*,1′*R*)-16b. The product was obtained in 90% yield starting from (2*R*,3*R*,3a*S*,1′*R*)-**14b**. (2*R*,3*R*,3a*S*,1′*R*)-**16b**: $[\alpha]^{20}_D = 19°$ (c = 1.07 in $CHCl_3$).

Methyl (2*RS*,3*RS*,3a*RS*)-2-[(1*SR*)-3-(Benzyloxy)-1-(mesyloxy)propyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate (16c). The same procedure described for the preparation of mesylate **10a** was used to prepare **16c** starting from alcohol **14c**. Compound **16c** was obtained as a colorless oil in 84% yield after purification by flash chromatography using hexane−ethyl acetate (1:1) as eluent. **16c**: IR (film) 1737, 1358, 1195 cm^{-1}; ^1H NMR (400 MHz, 250 K) δ 7.36 (m, 5 H), 4.93 (ddd, J = 8.1, 4.5, 3.5 Hz, 1 H), 4.51 (d, J = 11.5 Hz, 1 H), 4.40 (d, J = 11.5 Hz, 1 H), 4.40 (dd, J = 6.3, 4.5 Hz, 1 H), 3.69 (s, 3 H), 3.63−3.54 (m, 2 H), 3.28 (m, 1 H), 3.18 (dd, J = 10.1, 6.3 Hz, 1 H), 3.17 (s, 3 H), 2.41−2.31 (m, 2 H), 2.09−2.00 (m, 2 H), 1.89−1.79 (m, 1 H), 1.78−1.61 (m, 2 H), 1.58−1.33 (m, 2 H), 1.26−1.11 (m, 1 H); ^{13}C NMR (100 MHz, 250 K) δ 172.0, 139.3, 128.9, 128.5, 128.1, 81.0, 79.5, 73.1, 71.2, 65.9, 55.4, 54.3, 52.5, 38.2, 31.8, 28.9, 24.8, 23.5. Anal. Calcd for $C_{20}H_{29}NO_7S$: C, 56.19; H, 6.84; N, 3.28; S, 7.50. Found: C, 55.96; H, 6.90; N, 3.32; S, 7.39.

Methyl (2*RS*,3*RS*,3a*RS*)-2-[(1*RS*)-3-(Benzyloxy)-1-(mesyloxy)propyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate (16d). The same procedure described for the preparation of mesylate **10a** was used to prepare **16d** starting from alcohol **14d**. Compound **16d** was obtained as a colorless solid in 84% yield after purification by flash chromatography using hexane−ethyl acetate (1:1) as eluent. **16d:** mp 63−5 °C (ethyl acetate−hexane); IR (film) 1736, 1356, 1200 cm^{-1};

^{1}H NMR (400 MHz, 250 K) δ 7.36 (m, 5 H), 4.77 (td, J = 9.3, 2.7 Hz, 1 H), 4.49 (d, J = 11.8 Hz, 1 H), 4.43 (d, J = 11.8 Hz, 1 H), 4.32 (dd, J = 9.3, 5.1 Hz, 1 H), 3.66 (s, 3 H), 3.61−3.50 (m, 2 H), 3.30 (m, 1 H), 3.11 (s, 3 H), 2.91 (dd, J = 9.7, 5.1 Hz, 1 H), 2.43 (ddd, J = 12.2, 9.1, 2.9 Hz, 1 H), 2.36 (ddd, J = 12.0, 9.7, 2.5 Hz, 1 H), 2.07−1.92 (m, 2 H), 1.85−1.63 (m, 3 H), 1.60−1.46 (m, 1 H), 1.46−1.34 (m, 1 H), 1.26−1.13 (m, 1 H); ^{13}C NMR (100 MHz, 250 K) δ 171.9, 139.2, 128.9, 128.4, 128.1, 81.4, 79.7, 73.1, 71.6, 65.6, 55.2, 55.0, 52.5, 38.1, 31.1, 28.9, 24.8, 23.6. Anal. Calcd for $C_{20}H_{29}NO_7S$: C, 56.19; H, 6.84; N, 3.28; S, 7.50. Found: C, 56.07; H, 6.79; N, 3.24; S, 7.40.

(2*R*,3*R*,3a*R*,1′*R*)-16d. The product was obtained in 83% yield starting from (2*R*,3*R*,3a*R*,1′*R*)-**14d**. (2*R*,3*R*,3a*R*,1′*R*)-**16d**: $[\alpha]^{20}_D = -29°$ (c = 1.10 in $CHCl_3$).

Chemical Correlation of 13a with 20. A mixture of NaH (10 mg of a 50% dispersion in mineral oil, 0.21 mmol) and adduct **13a** (140 mg, 0.65 mmol) in THF (6 mL) was stirred at rt for 7 h. The solvent was exchanged by CH_2Cl_2 (4 mL), and the solution was washed with water (3 × 4 mL) and dried over anhydrous Na_2SO_4. Flash chromatography of the crude material using ethyl acetate as eluent yielded the following fractions: (i) **20**[16b] (8 mg, 0.04 mmol, 7% yield, 49% yield based on unrecovered **13a**); and (ii) **13a** (121 mg, 0.56 mmol).

Chemical Correlation of 14b with 21b. A mixture of NaH (15 mg of a 50% dispersion in mineral oil, 0.31 mmol) and adduct **14b** (129 mg, 0.37 mmol) in THF (4 mL) was heated at reflux for 8 h. The solvent was exchanged by CH_2Cl_2 (4 mL), and the solution was washed with water (3 × 4 mL) and dried over anhydrous Na_2SO_4. Flash chromatography of the crude material using hexane−ethyl acetate (1:1) as eluent yielded the following fractions: (i) **21b**[16a] (6 mg, 0.02 mmol, 5.5% yield, 24% yield based on unrecovered **14b**); and (ii) **14b** (101 mg, 0.29 mmol).

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Supporting Information Available: Full assignment of ^{1}H and ^{13}C NMR peaks of methyl (*E*)-6-methoxy-2-hexenoate, methyl (*E*)-6-methoxy-4-oxo-2-hexenoate, and compounds **4**, **10a**,**b**, **12a**,**b**, **13a**,**b**, **15a**,**b**,**d**, **16a**−**d**, **17a**−**d**, **18a**−**d**, and **19a**−**d**. Tables containing the most significant NMR data for adducts **9**−**13** and **14**−**19**. ORTEP drawing and details for the X-ray data acquisition for **15d** and **16d** (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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