[3 + 2] Cycloadditions between α,β-Unsaturated Esters or Nitroalkenes and Camphor-Derived Oxazoline *N*-Oxides: Experimental and Theoretical Study

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Oxazoline *N*-oxide **2** in the presence of α,β-unsaturated esters or nitroalkenes afforded the corresponding adducts with excellent regio- and stereoselectivities depending of the substitution pattern on the dipolarophile. Especially, inversion of regioselectivity was observed by switching from a 1,2-disubstituted to a 1,1-disubstituted α,β-unsaturated ester. This was not observed when nitroalkenes are used as dipolarophiles. An attempt to rationalize the observed selectivities by semiempirical calculations at RHF AM1 level is described. The cycloadduct **5e** has been used as the starting material in a total synthesis of the pheromone (−)-frontalin **12**.

Introduction

Asymmetric [3 + 2] cycloadditions of nitrile oxides and analogues thereof with alkenes have been developed in the recent years as a convenient alternative to the aldol addition reaction.[1] Recently, we have introduced the use of enantiomerically pure, camphor-derived oxazoline *N*-oxides as dipoles for the asymmetric [3 + 2] cycloaddition with a great variety of reactive alkenes[2] (Figure 1). This methodology, combined with a new method for the hydrolysis of the chiral auxiliary, has led to the preparation of aldol-type adducts,[2] and has been applied to the synthesis of β-lactones[3] and (+)-carbovir.[4] In an extensive study concerning the scope and applications of this cycloaddition reaction, we focused on the use of α,β-unsaturated esters and nitroalkenes since these very reactive dipolarophiles give rise to useful synthetic intermediates after functional group manipulation and hydrolysis. In the present communication, we wish to report our observations of the regio- and stereoselectivity obtained with diversely substituted α,β-unsaturated esters and nitroalkenes as well as theoretical calculations.

Results and Discussion

In a general procedure, 3-(hydroxyamino)isoborneol hydrochloride (**1**)[5] was treated with trimethyl orthoformate[6] (4 equiv) in the presence of 1 equiv of calcium carbonate, at 45 °C in either dichloromethane or toluene, to form the oxazoline *N*-oxide **2**. After 4 h, the dipolarophile **3a**−**g** was added, and the mixture was stirred at the appropriate temperature and time (see Table 1). After usual workup and purification, the cycloadducts **4a**−**g** and/or **5a**−**g** were isolated. The experimental results are summarized in Table 1.

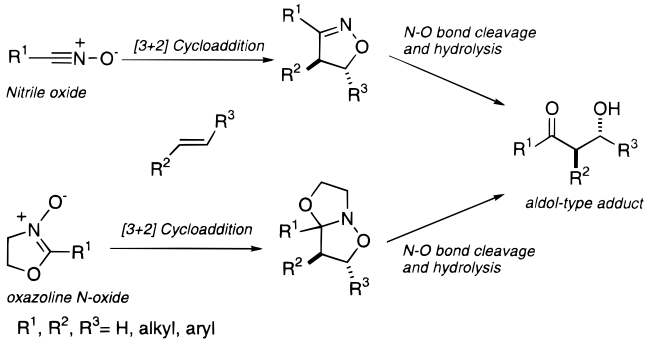

Figure 1.

The reaction proceeds in moderate to good yield (except for entry g) and proved to be highly regio- and stereoselective, giving in most cases a single product, except for entries a, d, and g. NMR analysis of samples taken during the course of the reaction showed no modification of product distribution in the crude mixture. No byproduct arising from side-reaction (apart from decomposition of the dipole **2**), e.g. anionic polymerization of the dipolarophile, radical coupling, or rearrangement, could be detected. The excess dipolarophile (especially nitro compounds) may be recovered if necessary in nearly quantitative yield. Therefore, the reaction products can be considered as kinetic products issued from a cycloaddition transition state, in which the dipolarophile approaches from the less hindered bottom face of the dipole.

To rationalize the experimental observations, the calculation of the frontier molecular orbital energies and

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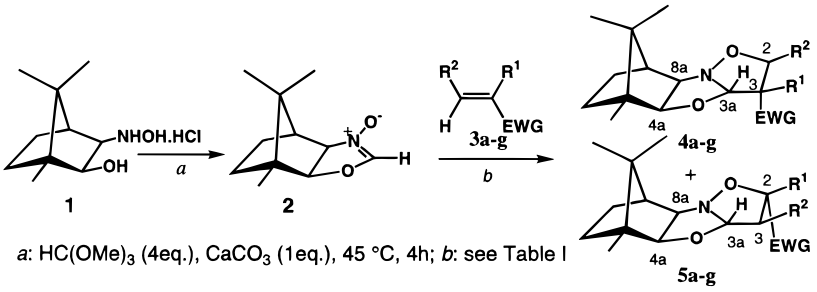
Scheme 1



Scheme 2

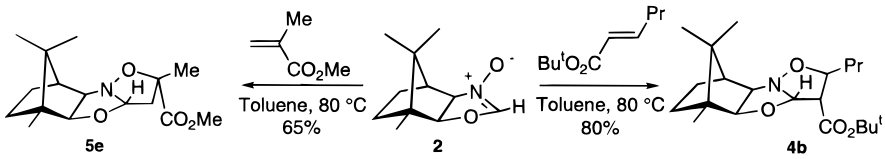
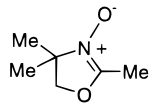


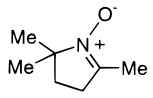
Table 1

entry	EWG	R^1	R^2	conditions	yield, %	**4**/**5**[a]	*endo*/*exo*[a,b]
a	CO_2Me	H	H	CH_2Cl_2, reflux, 3 h	53	85/15	75/25
b	NO_2	H	Bu^n	CH_2Cl_2, reflux, 2 h	70	>95/5	>95/5
c	CO_2Bu^t	H	Pr	toluene, 80 °C, 16 h	80	>95/5	>95/5
d	NO_2	Me	H	CH_2Cl_2, reflux, 4 h	58	>95/5	90/10
e	CO_2Me	Me	H	toluene, 60 °C, 2 h	65	>5/95	>95/5
f	NO_2	Me	Bu^n	toluene, 80 °C, 16 h	75	>95/5	>95/5
g	CO_2Bu^t	Me	Bu^n	toluene, 80 °C, 16 h	16	50/50	>95/5

[a] Determined by NMR analysis of the crude product. [b] For the major regiosomer in entries a−f; for both regioisomers in entry g.



2,4,4-trimethyl oxazoline *N*-oxide



2,2,5-trimethylpyrrolidine *N*-oxide

Figure 2.

coefficients of the reactants were performed at the RHF/AM1 level[7] using MOPAC program (Version 5.0).[8]

Coates and co-workers[6] have rationalized the enhanced reactivity of the 2,4,4-trimethyloxazoline *N*-oxide compared to the related 2,5,5-trimethylpyrroline *N*-oxide in terms of frontier orbital theory[9] (Figure 2). To compare with our results, we have performed FMO calculations of these two compounds at the AM1 level. The presence of the endocyclic oxygen atom in the oxazoline *N*-oxide reduces the frontier orbital separation, compared to the pyrrolidine *N*-oxide: it shifts the HOMO to higher energy (−8.51 to −8.41 eV) and the LUMO to lower energy (+0.69 to +0.59 eV). This allows for stronger interactions between the dipole HOMO and the dipolarophile LUMO as well as the dipole LUMO and the dipolarophile HOMO. Calculations applied on dipole **2** show that the HOMO (−8.58 eV) and LUMO (+0.56 eV) of **2** are slightly lower than the HOMO (−8.41 eV) and LUMO (+0.59 eV)

Table 2. FMO Energy Levels and Atom Coefficients in Dipole 2

	E[a]	O_1	N_2	C_3	O[b]
HOMO	−8.58	+0.64	−0.31	−0.57	+0.36
LUMO	+0.56	+0.37	−0.59	+0.65	−0.18

[a] The *E*(HOMO) and *E*(LUMO) are in eV. [b] The O atom adjacent to C_3.

of the 2,4,4-trimethyloxazoline *N*-oxide, respectively: this successfully explains the good reactivity of **2**. On the basis of these results, one might anticipate that oxazoline *N*-oxides such as **2** would show better reactivities and selectivities than the corresponding nitrones in the [3 + 2] cycloaddition reactions.

Frontier orbital energies and corresponding coefficients of *N*-oxide **2** and dipolarophiles **3a**−**g** are reported, respectively, in Tables 2 and 3 (Figure 3, Tables 2 and 3). The relative disposition of the frontier orbitals for dipole **2** (HOMO = −8.58 eV; LUMO = +0.56 eV) and dipolarophiles **3a**−**g** (HOMO about −10, −11 eV; LUMO about 0, −1 eV) suggests that, on the basis of the narrower HOMO−LUMO gap, the reactions are predominantly HOMO dipole-controlled reactions. However, it can be noted that the difference between O and C coefficients is more important in the LUMO (+0.37, +0.65, respectively) than in the HOMO (+0.64, −0.57, respectively) of the dipole **2**; consequently, in some cases, the LUMO dipole−HOMO dipolarophile interaction should not be neglected.

Experimentally, nitroalkenes show greater reactivity than α,β-unsaturated esters, as judged by reaction temperatures and times, and reactivity decreases when the substitution on double bond increases. The high electron-withdrawing character of the nitro group allows cycloaddition of 2-nitro-2-heptene **3f** to proceed with a good yield under relatively mild conditions (Table 1, entry f). In contrast, cycloaddition with the 1,1,2-trisubstituted unsaturated ester **3g** gives a disappointing 16% yield under the same conditions. FMO analysis (Table 3) shows that the substitution of the CO_2Me group in the dipolarophiles **3c**, **3e** and **3g** by a NO_2 group as in **3b**, **3d**, and **3f**, respectively, lowers to a much greater extent the LUMO energy level than the HOMO one (HOMO/LUMO = −10.51/−0.01, −10.47/+0.04 and −9.93/+0.17 eV instead of −11.27/−0.87, −11.21/−0.79 and −10.68/−0.73 eV). This fact explains the great reactivity of nitroalkenes

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Table 3. FMO Energy Levels and Atom Coefficients in Dipolarophiles 3a−g

entry	EWG	R^1	R^2		E[a]	C_1	C_2	C or N	O[b]	O[c]
a	CO_2Me	H	H	HOMO	−11.08	+0.68	+0.65	−0.05	−0.30	−0.10
				LUMO	+0.001	−0.48	+0.66	−0.43	+0.34	+0.17
b	NO_2	H	Me	HOMO	−11.27	+0.69	+0.55	−0.03	−0.15	−0.19
				LUMO	−0.87	−0.43	+0.63	−0.40	+0.33	+0.33
c	CO_2Me	H	Me	HOMO	−10.51	+0.67	+0.57	−0.02	−0.27	−0.10
				LUMO	−0.01	−0.48	+0.66	−0.40	+0.33	+0.16
d	NO_2	Me	H	HOMO	−11.21	+0.62	+0.63	−0.02	−0.15	−0.13
				LUMO	−0.79	−0.43	+0.62	−0.43	+0.34	+0.34
e	CO_2Me	Me	H	HOMO	−10.47	+0.61	+0.64	−0.02	−0.24	−0.07
				LUMO	+0.04	−0.48	+0.66	−0.42	+0.34	+0.16
f	NO_2	Me	Et	HOMO	−10.68	+0.63	+0.55	−0.01	−0.15	−0.14
				LUMO	−0.73	−0.43	+0.62	−0.41	+0.33	+0.33
g	CO_2Bu^t	Me	Et	HOMO	−9.93	+0.62	+0.57	0.	−0.24	−0.07
				LUMO	+0.17	−0.49	+0.66	−0.39	+0.31	+0.15

[a] The *E*(HOMO) and *E*(LUMO) are in eV. [b] The O atom in *cis* position compared to the C−C double bond. [c] The O atom in *trans* position compared to the C−C double bond.

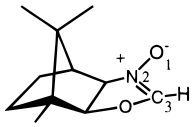

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Figure 3.

which should react, predominantly with their LUMO. Moreover, the addition of an electron-releasing alkyl substituent in the dipolarophile shifts its HOMO and LUMO to higher energy. Independently of steric effects, this is consistent with the observed experimental decrease of reactivity when substitution on the double bond increases.

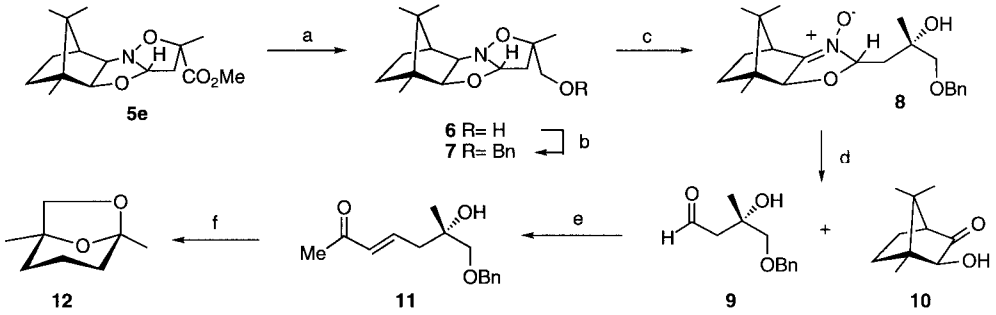
Some striking differences may also be observed in the selectivity of the cycloadditions with esters. Although reaction with methyl acrylate (Table 1, entry a) gives moderate regio- and stereoselectivities, reaction with disubstituted alkenes such as *tert*-butyl 2-pentenoate **3c** and methyl methacrylate **3e** occurred with complete regioselectivity, *but to give the opposite regioisomers* (Table 1, entries c and e, Scheme 2). FMO analysis shows that both HOMO or LUMO dipole-controlled reactions with the dipolarophiles **3a**, **3b**, **3c**, **3f**, **3g** (larger coefficient at carbon C_2 in the LUMO and larger coefficient at carbon C_1 in the HOMO) should lead to 4-substituted cycloadducts (Table 2). For **3d** and **3e** (larger coefficient at unsubstituted carbon C_2 in the LUMO and in the HOMO), the control of regioselectivity by the dipole HOMO (larger coefficient on the O heteroatom) and the dipolarophile LUMO (larger coefficient is at unsubstituted carbon C_2) will lead to 4-substituted cycloadduct, but the control of regioselectivity by the dipole LUMO (larger coefficient on the C atom) and the dipolarophile HOMO (larger coefficient is at unsubstituted C_2 carbon) will lead to 5-substituted cycloadduct. As mentioned above, on one hand, the addition of an electron-releasing alkyl substituent in the dipolarophile shifts its HOMO and LUMO to higher energy and on the other hand, in the HOMO of **3e** in contrast with **3c**, the larger coefficient is at the C_2 unsubstituted carbon. Reversal of regioselectivity with methyl methacrylate (Table 1, entry e) could be the consequence of the dipole LUMO−dipolarophile HOMO interaction which becomes more important with the addition of an alkyl group (Table 3).

In contrast with esters, nitroalkenes react with the dipole **2** (entries b, d, and f) with *consistent regioselectivity to give the cycloadducts of type* ***4****, whatever the substitution pattern on the double bond*. This remarkable selectivity may be explained by the fact that the strongly electron-withdrawing nitro substituent in the dipolarophiles considerably lowers the energy level of the LUMO orbital (about −0.7, −0.9 eV), favoring HOMO dipole-controlled reactions. Therefore, as mentioned above, in contrast with **3b** and **3f**, the larger coefficient is at unsubstituted carbon C_2 in the HOMO of **3d,** but the regioselectivity is not affected, in contrast with the esters, because only HOMO dipole-controlled reactions should occur and lead to formation of regioisomers **4**. The results of FMO calculations support the experimental data.

In both reactions, *endo* and facial selectivities were complete, except in the reaction with 2-nitropropene (Table 1, entry d) where a small amount of the *exo* isomer is also obtained. This minor compound is easily removed by chromatography. FMO analysis (Table 3) reveals that the coefficients at the central nitrogen and at the endocyclic oxygen in the dipole HOMO (−0.3 and +0.4, respectively) and at the carbon (or nitrogen) and at the oxygen of the COOR (or NO_2) group in the dipolarophile LUMO (about −0.4 and +0.3, respectively) have the same sign. This suggests that this attractive interaction can lead to stabilizing secondary orbital interaction and explains the preferred *endo* selectivity in those cycloadditions.

These calculations point out that the origin of the regioselectivity is certainly the stabilization in the transition state due to the favorable overlap of the π orbitals, that the preferred *endo* stereoselectivity is due to the stabilizing secondary interactions between the *pz* of the central nitrogen and endocyclic oxygen in the dipole and the *pz* of the CO_2 (or NO_2) group of the dipolarophile, and that the reversal of regioselectivity with methyl methacrylate might be the consequence of the dipole LUMO−dipolarophile HOMO interaction which becomes more important with the addition of an alkyl group. Moreover, the regioselectivity with methyl methacrylate could also be explained by steric effects with transition structure model considerations: the interaction of the *exo* methyl substituent on the alkene with the hydrogen borne by the C_3 of the dipole probably disfavors the *endo* 4-substituted cycloadduct by comparison with the *endo* 5-substituted one; however, this interaction is not well evaluated in AM1 calculations. It is possible that the induced torsion in the developing five-membered ring in the transition state destabilizes the formation of the cycloadduct **4e**, leading to the formation of **5e**, arising from a less hindered transition state. The reversal of regioselectivity is not observed in the cycloaddition with 2-nitropropene **3d** (in which the larger coefficient in the

Scheme 3



[a]: $LiAlH_4$, Et_2O, 0 °C, 30 min, 93%; [b]: BnBr, cat; nBu_4I, THF/DMF, 0 °C to RT, 4h, 85%;
[c]: 3.5 eq. *m*CPBA, Et_2O, RT, 1h; [d]: 2N HCl, THF, RT, 5 min, 70% overall (+80% **10**);
[e]: $Ph_3P{=}CHCOCH_3$, MeCN, reflux, 4h, 71% (+ 15 % SM); [e]: H_2 (1 atm), Pd/C, MeOH, 99%.

HOMO is at the C_2 unsubstituted carbon as in **3e**) because the dipole HOMO−dipolarophile LUMO interaction remains predominant, this being due to the high electron-withdrawing character of the nitro group. Moreover, the presence of a small amount of the *exo* isomer supports the above mentioned steric effect of the *exo* substituent on the nitroalkene with the hydrogen borne by the C_3 carbon of the dipole (Figure 4).

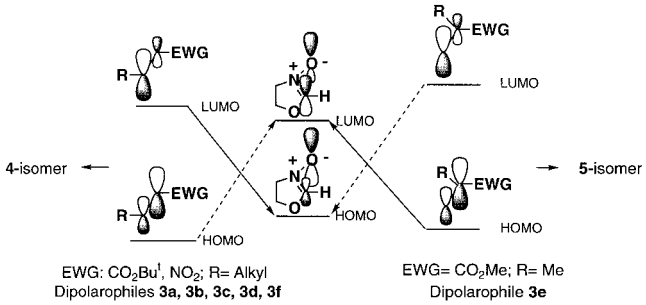


Figure 4.

Hydrolysis of 5e. Total Synthesis of Frontalin. Despite being obtained with an "reversed" regioselectivity, the cycloadduct **5e** has an interesting potential in synthesis since the introduction of a chiral tertiary alcohol with two different neighboring functional groups could be useful for the assembly of polyoxygenated molecules. We have therefore undertaken the hydrolysis of the chiral auxiliary in **5e** and used the corresponding product in total synthesis of the natural pheromone (−)-frontalin **12**[10] (Scheme 3).

Previous studies showed it is possible to reduce the ester function in cycloadducts leaving the N−O bond unaffected; therefore, reduction of **5e** ($LiAlH_4$, Et_2O) followed by protection of the primary alcohol **6** as its benzyl ether (BnBr, nBu_4I, THF/DMF) gave compound **7** in an excellent yield and in a complete chemoselective fashion. This product was subjected to the oxidative hydrolysis procedure developed in our laboratory:[2] treatment with excess *m*-chloroperoxybenzoic acid to give the intermediate nitrone **8**, followed by acidic hydrolysis with 2 N HCl in THF afforded the aldehyde **9** in 71% isolated yield (overall yield for two steps), together with the recovered ketol **10** (80% recovery). The lower yield of **9** is due to partial elimination of the tertiary alcohol; this side-reaction becomes more important when hydrolysis reaction time is extended. This aldehyde has already been prepared (as its antipode) by Monneret and coworkers and used as an intermediate in the total synthesis of frontalin.[11] Therefore the remaining steps have been carried out as described by these authors: treatment of **9** with (triphenylphosphoranylidene)acetone in refuxing acetonitrile gave the unsaturated ketone **11** in 71% yield (with 15% recovered starting material). Hydrogenation reaction (1 atm, Pd/C) gave in quantitative yield (−)-frontalin **12**, whose spectral data were in complete agreement to those reported in the literature. This short and stereoselective synthesis of frontalin **12** has shown the potential of cycloaddition reactions with oxazoline *N*-oxide in the preparation of small, densely functionalized chiral molecules such as the aldehyde **9**.

Conclusion

The experimental results obtained in this study have revealed the great versatility of the asymmetric [3 + 2] cycloadditions of oxazoline *N*-oxides to give good yields and excellent regio- and stereoselectivities with *disubstituted* α,β-unsaturated esters or with diversely substituted nitroalkenes. In comparison, nitrile oxides are poorly regioselective with these dipolarophiles.[1] The use of cycloadduct **5e** in the synthesis of the natural product fontalin **12** has illustrated the application of these cycloadditions in synthesis. Furthermore, it has given additional confirmation of the structure and purity of the starting cycloadduct. Other synthetic applications of asymmetric [3 + 2] cycloadditions with oxazoline *N*-oxides are currently under investigation in our laboratory.

Experimental Section

Generalities. ^1H and ^{13}C NMR spectra were recorded at 200 or 250 MHz and 50 or 62.5 MHz, respectively. Optical rotations were recorded at 25 °C. Chromatographic purifications were performed on 230−400 mesh silica gel (Merck 9385) using the indicated solvent system. Dichloromethane, acetonitrile, DMF, and trimethyl orthoacetate were distilled from

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calcium hydride. Toluene, diethyl ether, and THF were distilled from sodium metal/benzophenone ketyl. Chloroform used for optical measurements was filtered through basic alumina before use. *tert*-Butyl 2-hexenoate and *tert*-butyl 2-methyl-2-pentenoate were prepared by esterification of the commercially available acids. 2-Nitropropene was prepared by dehydration (phthalic anhydride, 150 °C) of commercial 2-nitro-1-propanol. 1-Nitro-1-hexene and 2-nitro-2-heptene were prepared by Henry condensation (Al_2O_3) of nitromethane and nitroethane with valeraldehyde, followed by dehydration (PPh_3, CCl_4). Methyl acrylate and methyl methacrylate were obtained from commercial sources. All nonaqueous reactions were performed under an argon atmosphere using oven-dried glassware.

General Experimental Procedure for the Cycloaddition Reactions. A suspension of 3-(hydroxylamino)isoborneol hydrochloride **1** (1 equiv) and powdered calcium carbonate (l equiv) in either dichloromethane or toluene (5 mL/mmol) was heated at 45 °C with stirring, and trimethyl orthoacetate (4 equiv) was added with syringe. The mixture was stirred at 45 °C for 4 h, and then the dipolarophile was added (4 equiv). The mixture was vigorously stirred at the appropriate temperature and time (see Table 1). The completion of the reaction was monitored by TLC. After cooling to room temperature, the mixture was filtered through a pad of Celite and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10% ethyl acetate/heptane) to give the pure cycloadduct.

(3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-5,10,10-Trimethyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-carboxylic Acid Methyl Ester (4a). Reaction was performed in refluxing dichloromethane for 4 h after adding methyl acrylate. ^{1}H NMR analysis of the crude product showed the presence of three cycloadducts **4a**, **5a**, and *exo*-**4a** in the ratio (60:20:15) according to the integration of the C_{3a} proton (**4a**: 5.51 ppm; **5a**: 5.37 ppm; *exo*-**4a**: 5.29 ppm). The combined yield is 53%. Careful chromatographic purification allows isolation of some pure **4a** (R_f: 0.20) together with mixed fractions with **5a** and *exo*-**4a** (R_f: 0.18). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 5.51 (lH, d, J = 7.5 Hz), 4.16 (lH, dd, J = 8 and 10 Hz), 3.95 (lH, dd, J = 1 and 10 Hz), 3.88 (lH, d, J = 7 Hz), 3.72 (3H, s), 3.42 (lH, ddd, J = 1, 7.5 and 10 Hz), 3.22 (lH, d, J = 7 Hz), 2.09 (lH, d, J = 4,5 Hz), 1.68 and 1.35 (4H, 2m), 0.91 and 0.73 (9H, 2s); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 169.3, 98.1, 90.2, 75.5, 66.9, 53.2, 52.4, 49.2, 48.7, 46.0, 31.5, 25.6, 22.3 19.0, 10.9; mass (IC NH_3): 282 (MH^+); $[\alpha]^{20}_D$ = −121.6 (c = 1.53, $CHCl_3$). Anal. Calcd for $C_{15}H_{23}NO_4$, MW: 281.35486; Cald: C: 64.04%; H: 8.45%; N: 4.98%. Found: C: 64.21%; H: 8.45%; N: 4.82%.

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-2-Butyl-3-nitro-5,10,10-trimethyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole (4b). Reaction was performed in refluxing dichloromethane for 2 h after adding l-nitro-1-hexene; yield: 70%. The product **4b** was obtained as a single stereomer. This product was not very stable on storage, and therefore combustion analysis could not be obtained. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 5.55 (1H, d, J = 7 Hz), 4.80 (lH, dd, J = 7 and 8 Hz), 4.65 (lH, dt, J = 6 and 8 Hz), 4.05 (lH, d, J = 7.5 Hz, 3.45 (lH, d, J = 7.5 Hz), 2.10 (lH, d, J = 4.5 Hz), 1.80−1.30 (10H, m), 0.90 (3H, t, J = 7 Hz), 0.95, 0.88 and 0.80 (9H, 3s); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 96.4, 92.5, 91.4, 78.0, 75.7, 49.1, 48.7, 45.8, 31.3, 30.6, 27.3, 25.2, 22.4, 22.0, 18.7, 13.7, 10.6; mass (IC NH_3): m/z: 325 (MH^+); $[\alpha]^{20}_D$ = 161 (c = 1.47, $CHCl_3$); high-resolution mass spectrum, calcd for $C_{17}H_{28}N_2O_4$; calcd: 324.20489; found: 324.20491.

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-5,10,10-Trimethyl-2-propyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-carboxylic Acid 1,1-Dimethylethyl Ester (4c). Reaction was performed in toluene at 80 °C for 18 h after adding *tert*-butyl 2-hexenoate. Yield: 80%. The product **4c** was obtained as a single stereomer. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 5.37 (lH, d, J = 7.5 Hz), 4.35 (lH, dt, J = 10.5 and 6 Hz), 3.72 (lH, d, J = 7.5 Hz), 3.25 (lH, d, J = 7.5 Hz), 2.95 (lH, dd, J = 10.5 and 7.5 Hz), 2.02 (lH, d, J = 4.5 Hz), 1.60−1.10 (8H, m), 1.42 (9H, s), 0.95 (3H, t), 0.90 and 0.71 (6H and 3H, 2s); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 167.7, 98 1, 89.1, 80.9, 77.5, 75.2, 58.4, 48.6, 47.7, 45.3, 33.7, 30.8, 27.5, 25.9, 21.6, 18.6, 18.4, 13.6, 10.1; mass (IC, NH_3): 366 (MH^+); $[\alpha]^{20}_D$ = −129 (c = 2.5, $CHCl_3$). Anal. Calcd for $C_{21}H_{35}NO_4$, MW: 365.25659; Calcd: C: 68.99%; H: 9.66%; N: 3.83%. Found: C: 68.66%; H: 9.66%; N: 3.91%.

(3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-3-Nitro-3,5,10,10-tetramethyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole (4d). Reaction was performed in refluxing dichloromethane for 4 h after the addition of 2-nitropropene. The crude product was purified by chromatography. First to elute was **4d** (R_f: 0.35), followed by a small amount of *exo*-**4d** (R_f: 0.29). Yield: 58%. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 4.94 (lH, s), 4.73 (lH, d), 3.94 (lH, d, J = 7.5 Hz), 3.79 (lH, d, J = l0 Hz), 3.42 (lH, d, J = 7.5 Hz), 2.09 (lH, d, J = 4.5 Hz), 1.78 (3H, s), 1.80 and 1.65 (4H, 2m), 0.87, 0.83, 0.77; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 102.8, 94.9, 91.4, 75.6, 72.1, 49.2, 48.9, 45.8, 31.4, 25.5, 22.8, 22.6, 18.9, 10.8; mass (IC NH_3): m/z: 301 (MNH_4^+), 283 (MH^+); $[\alpha]^{20}_D$ = −202.1 (c = 1.89, $CHCl_3$). Anal. Calcd for $C_{14}H_{22}N_2O_4$, MW: 282.34244; Calcd: C: 59.56%; H: 7.85%; N: 9.92%. Found: C: 59.71%; H: 8.11%; N: 9.42%.

(2*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-2,5,10,10-Tetramethyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole-2-carboxylic Acid Methyl Ester (5e). Reaction was performed in toluene at 80 °C for 2 h after adding methyl methacrylate. Yield: 65%. The product **5e** was obtained as a single stereomer. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 5.48 (lH, dd, J = 4.2 and 6.6 Hz,), 3.92 (lH, d, J = 7.5 Hz), 3.80 (3H, s), 3.65 (lH, d, J = 7.5 Hz), 2.85 (lH, dd, J_{gem} = 13.5 Hz and J_{trans} = 4.2 Hz), 2.25 (lH, dd, J_{gem} = 13.5 Hz and J_{cis} = 6−6 Hz), 2.05 (lH, d, J = 4.5 Hz), 1.70 and 1.40 (4H, 2m), 1.48 (3H, s), 0.95, 0.94, and 0.79 (9H, 3s); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 174.0, 98.1, 88.4, 83.9, 75.9, 52.5, 49.0, 48.1, 45.6, 44.3, 31.5, 25.5, 24.5, 22.2,19.0, 10.7; mass (IC NH_3): m/z 296 (MH^+); $[\alpha]^{20}_D$ = −32.2 (c = 1.42, $CHCl_3$). Anal. Calcd for $C_{16}H_{25}NO_4$, MW: 295.3482; Calcd: C: 65.06%; H: 8.53%; N: 4.74%. Found: C: 64.77%; H: 8.71%; N: 4.77%.

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-2-Butyl-3-nitro-3,5,10,10-trimethyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole (4f). Reaction was performed at 80 °C in toluene for 16 h after adding 2-nitro-2-heptene. Yield: 75%. The product **4f** was obtained as a single stereomer. ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 4.96 (lH, s, C_{3a}-H), 4.77 (lH, t, J = 6 Hz, C_2-H), 4.00 (lH, d, J = 7.5 Hz), 3.45 (lH, d, J = 7.5 Hz), 2.10 (lH, d, J = 4.5 Hz), 1.63 (3H, s), 1.80−1.30 (10H, m), 0.90 (3H, t, J = 7 Hz), 0.90, 0.85, and 0.80 (9H, 3s); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 103.9, 95.9, 91.2, 79.6, 76.6, 49.3, 48.7, 45.6, 31.3, 28.2, 26.5, 25.4, 22.6, 22.1, 18.7, 17.8, 13.8, 10.7; mass (IC NH_3): m/z: 339 (MH^+); $[\alpha]^{20}_D$ = −172 (c = 1.1, $CHCl_3$). Anal. Calcd for $C_{18}H_{30}N_2O_4$, MW: 338.22054; Calcd: C: 63.88%; H: 8.93%; N: 8.28%. Found: C: 64.23%; H: 9.24%; N: 8.41%.

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-2-Ethyl-3,5,10,10-tetramethyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-carboxylic Acid 1,1-Dimethylethyl Ester (4g) and (2*R*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-3-Ethyl-2,5,10,10-tetramethyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2*b*]benzoxazole-2-carboxylic Acid l,l-Dimethylethyl Ester (5g). Reaction was performed in toluene at 80 °C. The reaction was stopped 16 h after adding (*E*)-*tert*-butyl 2-methyl-2-pentenoate (no further evolution and degradation products were observed). Purification of the crude product gave first **4g** (yield: 8%; R_f: 0.37), followed by **5g** (yield: 8%; R_f: 0.28).

4g: ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 4.84 (lH, s), 4.33 (lH, dd, J = 7 Hz), 3.87 (lH, d, J = 7.5 Hz), 3.35 (lH, d, J = 7.5 Hz), 2.04 (lH, d, J = 4.5 Hz), 1.67 and 1.49−1.35 (6H, m), 1.42 (9H, s, Bu^t), 1.15 (3H, s), 0.92 (3H, t, J = 7 Hz), 0.84 and 0.76 (9H, 2s); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 170.8, 107.3, 89.9, 81.7, 81.4, 76.9, 59.4, 49.5, 48.6, 45.7, 31.6, 28.1, 25.8, 22.3, 20.7, 19.0, 11.1, 10.9; mass (IC NH_3): 366 (MH^+); $[\alpha]^{20}_D$ = −125.3 (c = 1, $CHCl_3$); high-resolution mass spectrum, calcd for $C_{21}H_{35}NO_4$: calcd: 365.2566; found: 365.2563.

5g: ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 4.91 (lH, d, J = 7.5 Hz), 4.01 (lH, d, J = 7.5 Hz), 3.66 (lH, d, J = 7.5 Hz), 2.48 (lH, dt), 2.01 (lH, d, J = 4.5 Hz), 1.63−1.41 (6H, m), 1.43 (9H,

s), 1.28 (3H, s), 0.95 (3H, masked t), 0.93 and 0.87 (9H, 2s); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 172.9, 103.1, 87.9, 87.4, 81.9, 75.4, 52.6, 48.8, 48.1, 46.4, 31.9, 28.0, 25.4, 22.3, 20.7, 19.7, 19.6, 12.3, 10.9; mass (IC NH_3): 366 (MH^+); $[\alpha]^{20}_D$ = −49.6 (c = 1, $CHCl_3$); high-resolution mass spectrum, calcd for $C_{21}H_{35}NO_4$: calcd: 365.2566; found: 365.2573.

(2*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-2-(Hydroxymethyl)-2,5,10,10-Tetramethyl-5,8-methano-octahydro-2*H*-isoxazolo[3,2-*b*]-benzoxazole (6). A solution of the cycloadduct **5e** (1.06 g, 3,6 mmol) in diethyl ether (30 mL) was cooled to 0 °C, and lithium aluminum hydride (402 mg, 10.1 mmol, 3 equiv) was added portionwise. The gray suspension was stirred at 0 °C for 30 min and then hydrolyzed by careful addition of a saturated aqueous sodium sulfate solution until a white solid separates from the colorless solution. The mixture was filtered through a pad of Celite, rinsing with ether; the filtrate was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give the alcohol **6** as a white solid, sufficientely pure for the next reaction (893 mg; yield: 93%). An analytical sample was obtained by chromatography.

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 5.48 (1H, dd, J = 6.6 and 7 Hz), 4.02 (lH, d, J = 7.5 Hz), 3.47 (2H, broad s), 3.33 (lH, d, J = 8 Hz), 2.59 (1H, exchangeable with D_2O), 2.20 (lH, dd, J_{gem} = 13.5 Hz and J_{trans} = 7 Hz), 1.96 (lH, d, J = 4.5 Hz), 1.89 (lH, dd, J_{gem} = 13.5 Hz and J_{cis} = 6.6 Hz), 1.60, 1.31, and 0.85 (4H, 3m), 1.14 (3H, s_2), 0.90, 0.87 and 0.72 (9H, 3s); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 98.5, 87.8, 85.7, 78.8, 66.5, 48.7, 48.0, 46.3, 39.6, 31.7, 25.5, 23.6, 22.2, 19.4, 10.8; mass (IC NH_3): m/z 268 (MH^+); $[\alpha]^{20}_D$ = −84.3 (c = 1.57, $CHCl_3$). Anal. Calcd for $C_{15}H_{25}NO_3$, MW: 267.1834; Calcd: C: 67.37%; H: 9.43%; N: 5.24%. Found: C: 67.28%; H: 8.97%; N: 5.53%.

(2*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-2-[[(Phenylmethyl)oxy]methyl]-2,5,10,10-tetramethyl-5,8-methanooctahydro-2*H*-isoxazolo-[3,2-*b*]benzoxazole (7). A suspension of oil-free sodium hydride (134 mg, 4.18 mmol, 1.25 equiv) in THF/DMF (15 mL/5 mL) was cooled to 0 °C with stirring, and a solution of the alcohol **6** (893 mg, 3.34 mmol) in THF (10 mL plus 5 mL rinse) was added dropwise. The mixture was stirred 30 min at 0 °C, and then a catalytic amount of tetra-*n*-butylammonium iodide was added, followed by benzyl bromide (0.5 mL, 4.18 mmol, 1.25 equiv). The cooling bath was removed, and the white suspension was stirred at room temperature for 4 h. The reaction mixture was quenched by addition of saturated ammonium chloride solution, poured onto ice, and extracted with diethyl ether (100 mL). The organic phase was washed successively with 5% $NaHCO_3$ solution, water, and brine and then dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (20% ethyl acetate/heptane) to give the benzyl ether **7** as a nearly colorless oil (994 mg; yield: 85%). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 7.30 (5H, broad s), 5.48 (1H, dd, J = 6.6 and 7 Hz), 4.61 (2H, AB system with J = 4 Hz), 3.92 (lH, d, J = 7.5 Hz), 3.49 (lH, d, J = 8 Hz), 3.44 (2H, s), 2.33 (lH, dd, J_{gem} = 13.5 Hz and J_{trans} = 7 Hz), 1.98 (lH, partially masked dd, J_{gem} = 13.5 Hz and J_{cis} = 6.6 Hz), 1.95 (lH, d, J = 4.5 Hz), 1.57 and 1.39 (4H, 2m), 1.26 (3H, s), 0.94, 0.89 and 0.77 (9H, 3s); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 183.1, 128.3, 128.0, 127.6, 127.5, 98.0, 87.7, 84.9, 76.0, 74.4, 73.3, 48.5, 47.7, 46.1, 40.5, 31.6, 25.1, 24.4, 22.1, 19.3, 10.7; mass (EI 70 eV): m/z 357 ($MH^{+\bullet}$), 328, 236, 196, 195, 152, 107, 91 (100%); $[\alpha]^{20}_D$ = −61.5 (c = 0.95, $CHCl_3$). Anal. Calcd for $C_{22}H_{31}NO_3$, MW: 357.4973; Calcd: C: 73.92%; H: 8.75%; N: 3.92%; Found: C: 73.84%; H: 8.51%; N: 3.83%.

(*S*)-3-Hydroxy-3-methyl-4-[(phenylmethyl)oxy]butanal (9). *m*-Chloroperoxybenzoic acid (1.38 g, 8 mmol, 3.5 equiv) was added portionwise to a stirred solution of the benzyl ether **7** (812 mg, 2.27 mmol) in diethyl ether (25 mL). The clear and colorless solution was stirred at room temperature for 1 h and then quenched by addition of an aqueous 10% sodium bicarbonate/10% sodium thiosulfate solution and vigorous stirring for 20 min. The mixture was decanted, and the organic phase was washed with saturated sodium carbonate solution and then with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude nitrone **8** as a white solid (crude yield >95%), which was used immediately in the next reaction.

The crude nitrone **8** was dissolved in THF (5 mL) with strirring, and a 2 N hydrochloric acid solution (5 mL) was added (exothermic reaction). The turbid solution cleared within 10 min whereupon it was neutralized with saturated sodium carbonate solution and extracted with ethyl acetate. The organic phase was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by silica gel (20% ethyl acetate/heptane); first to elute was the recovered ketol **10** (80% recovery), followed by the aldehyde **9** (332 mg; 71% yield) which was obtained as a yellow oil.

^{1}H NMR (200 MHz, C_6D_6): δ (ppm) 9.62 (1H, t, J = 2 Hz), 7.31 (5H, broad s), 4.18 (2H, s), 3.04 (2H, d, J = 2 Hz), 2.70 (1H, broad s, exchangeable with D_2O), 2.22 (1H, ddd, J_{gem} = 16 Hz and J_{1-2} = 2 Hz), 1.16 (3H, s); ^{13}C NMR (50 MHz, C_6D_6): δ (ppm) 202.1, 138.5, 128.7, 128.0, 77.5, 73.5, 71.6, 52.3, 25.1; mass (IC NH_3): m/z 208 (MH^+); $[\alpha]^{20}_D$ = −8.5 (c = 0.85, $CHCl_3$) (lit:[11] −8 (c = 1, $CHCl_3$)). Anal. Calcd for $C_{12}H_{16}O_3$, MW: 267.1834; Calcd: C: 69.21%; H: 7.74%. Found: C: 68.86%; H: 7.47%.

(*S*)-6-Hydroxy-6-methyl-7-[(phenylmethyl)oxy]-3-hepten-2-one (11). A solution of the aldehyde **9** (270 mg, 1.3 mmol) and (triphenylphosphoranylidene)acetone (656 mg; 2.08 mmol, 1.6 equiv) in acetonitrile (5 mL) was stirred at reflux for 3 h and then cooled and concentrated in vacuo. The residue was purified by chromatography (35% ethyl acetate/heptane); first to elute was the recovered starting material (40 mg, 15% recovery), followed by the ketone **11** which was isolated as a pale yellow oil (227 mg; yield 71%).

^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 7.31 (5H, broad s), 6.80 (1H, dd, J_{trans} = 16 Hz and J_{4-5} = 7 Hz), 6.05 (1H, d, J_{trans} = 16 Hz), 4.53 (2H, s), 3.30 (2H, s), 2.53 (1H, broad s, exchangeable with D_2O), 2.44 (2H, m), 2.20 (3H, s), 1.16 (3H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 198.7, 143.9, 137.8, 134.1, 128.5, 127.9, 127.8, 76.9, 73.5, 72.0, 42.4, 26.8, 24.1; mass (EI 70 eV): m/z 246 ($M^{+\bullet}$), 231 ($M^{+\bullet}$ − Me), 91 (100%); $[\alpha]^{20}_D$ = −14.4 (c = 1.51, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}O_3$, MW: 248.32485; Calcd: C: 72.55%; H: 8.12%. Found: C: 72.38%; H: 8.14%.

(1*S*,5*R*)-1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octane ((−)-frontalin) (12). A solution of the ketone **11** (183 mg, 0.74 mmol) in methanol (2 mL) containing palladium on carbon (30 mg) was stirred overnight under 1 atm of hydrogen. The black suspension was filtered through Celite, and water was added to the filtrate which was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. Careful evaporation of the solvent gave the title compound as a colorless liquid (103 mg, 99% yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm): 1.33 (3H, s, Me-C_5), 1.45 (3H, s, Me-C_1), 1.52−1.67 and 1.75−1.90 (5H and 1H, m, C_2-H × 2, C_3-H × 2 and C_4−H × 2), 3.46 (1H, dd, one of C_7-H), 3.92 (1H, dd, one of C_7-H); in C_6D_6, the signal of Me-C_5 shifts to 1.1 ppm and the signal of Me-C_1 to 1.53 ppm; in the presence of 1 equiv of Eu(hfc)$_3$, the latter signal shifts to a single peak at 2.40 ppm. No peak corresponding to the other enantiomer could be detected. Therefore, synthetic **12** was considered to be enantiomerically pure within the detection range of ^{1}H NMR spectroscopy. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 108.2 (C_5), 80.1 (C_1), 74.3 (C_7), 34.6 and 34.0 (C_2 and C_4), 24.8 (Me-C_5), 23.2 (Me-C_1), 18.1 (C_3). $[\alpha]^{20}_D$ = −51.2 (c = 2.23, Et_2O); lit.[10] −53 (c = 1.33, Et_2O); mass (EI 70 eV): m/z: 142 ($M^{+\bullet}$), 127; HRMS, calcd for $C_8H_{14}O_2$, MW: 142.0994; found: 142.0991.

Supporting Information Available: NMR spectra of all cycloadducts and of compounds **6**, **7**, **9**, **11**, and **12** (28 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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