[2 + 3] Cycloadditions of Enantiomerically Pure Oxazoline *N*-Oxides: An Alternative to the Asymmetric Aldol Condensation

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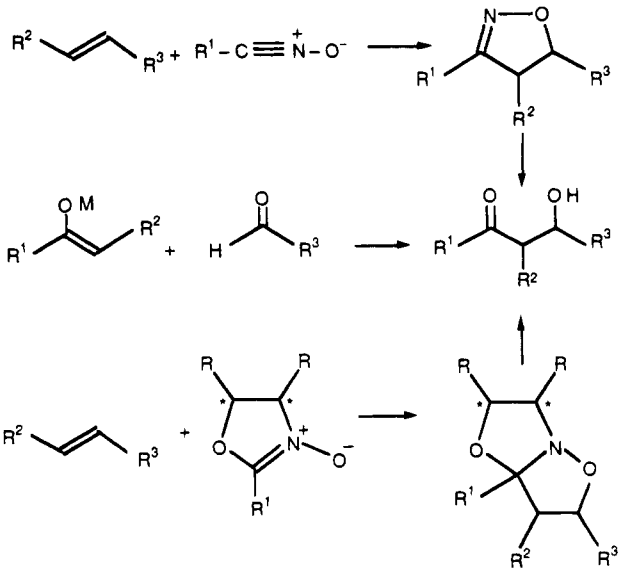
A series of camphor-derived oxazoline *N*-oxides were obtained by condensation of the appropriate orthoesters with (+)-3-(hydroxyamino)borneol (**8**). These unstable dipoles were used without isolation in various [2 + 3] asymmetric cyclocondensations. The regio- and diastereoselectivities of these reactions were good to excellent. After functional group transformations, adducts were cleaved by a two--step sequence (*i.e.*, oxidation followed by acidic hydrolysis) giving β-hydroxy ketones and (+)-3-(hydroxyimino)borneol (**19**). Asymmetric synthesis of (+)-1,7-dioxaspiro[5.5]-undecan-4-ol, a pheromone of *Dacus oleae*, was achieved as an application of this new method.

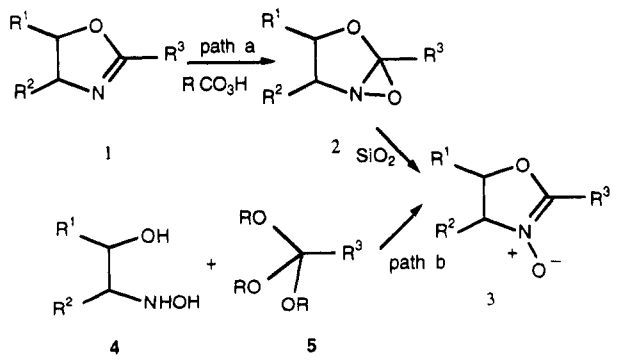
Introduction

Asymmetric aldol condensation[1,2] is the method of choice for the stereocontrolled elaboration of polyacetate- and polypropionate-derived natural products.[3] Concurrently during the past 10 years the [2 + 3] cycloaddition of nitrile oxides to alkenes appeared as an alternative[4] to the classical aldol condensation (Scheme 1). Thus, enantioselective syntheses of aldols have been effected using optically active alkenes as dipolarophiles. However, the use of optically active nitrile oxides led generally to less stereoselective cycloadditions.[5] Considering the large number of natural products containing β-hydroxy carbonyl units, the development of new stereoselective methods seemed to be worthy of investigation. Enantiomerically pure oxazoline *N*-oxides, which can be considered as chiral chemical equivalents of nitrile oxides, seemed to be good candidates for such asymmetric cycloadditions (Scheme 1). These dipoles can be prepared following two complementary methods. According to Keana,[6] peracid oxidation of oxazolines **1** afforded oxaziridinooxazolidines **2** which were in turn isomerized on silica gel to oxazoline *N*-oxide **3** (path a, Scheme 2). These dipoles can also be obtained in one step by direct condensation of β-hydroxylamino alcohols **4** with orthoesters **5** or amide acetals as described by Coates[7,8] (path b, Scheme 2).

Scheme 1



Scheme 2



Achiral oxazoline *N*-oxides, in the presence of various electron poor dipolarophiles, gave rise to [2 + 3] cycloadducts. However, with unsymmetrical dipolarophiles such as acrylonitrile or methyl acrylate cycloadditions showed poor regio- and stereoselectivity.[7] In order to overcome this drawback, an intramolecular version of this reaction

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Table 1

entry	dipole R^1	dipolarophile R^2; R^3	solvent, temp (°C) (time (h))	adducts yield[a] (%)	**10a**	**10b**	**11a + 11b**
1	Me (**9a**)	CN; H (**7a**)	CH_2Cl_2 (3)	49	70	25	5
2	Me (**9a**)	CO_2Me; H (**7b**)	CH_2Cl_2, 40 (18)	50	60	25	15
3	Me (**9a**)	CO_2Me; Me (**7c**)	$C_6H_5CH_3$, 80 (5)	53	100	0	0
4	Me (**9a**)	CO_2Bn; Me (**7d**)	$C_6H_5CH_3$, 80 (2)	52	100	0	0
5	Pr (**9b**)	CO_2Bn; Me (**7d**)	CH_2Cl_2, 40 (24)	52	100	0	0
6	Pr (**9b**)	CO_2Bn; Me (**7d**)	$C_6H_5CH_3$, 80 (1.5)	50	100	0	0
7	Pr (**9b**)	CO_2Me; Pr (**7e**)	$C_6H_5CH_3$, 80 (18)	63	100	0	0
8	Pr (**9b**)	$CO_2{}^t$Bu; Pr (**7f**)	CH_2Cl_2, 40 (48)	53	100	0	0
9	Me (**9a**)	SO_2Ph; Me (**7g**)	CH_2Cl_2, 40 (60)	42	100	0	0
10	Me (**9a**)	SO_2Ph; $(CH_2)_2OBn$, (**7h**)	CH_2Cl_2, 40 (24)	30	100	0	0
11	Me (**9a**)	H; $(CH_2)_2OBn$ (**7i**)	$C_6H_5CH_3$, 100 (4)	50	100	0	0
12	$(CH_2)_4OBn$ (**9c**)	SO_2Ph; $(CH_2)_2OBn$ (**7h**)	CH_2Cl_2, 40 (40)	25	100	0	0
13	$(CH_2)_4OBn$ (**9c**)	H; $(CH_2)_2OBn$ (**7i**)	$C_6H_5CH_3$, 80 (60)	23	100	0	0

[a] Yields were calculated for two steps: preparation of oxazoline *N*-oxides and cycloadditions.

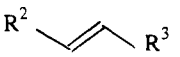
has been developed in our laboratory.[9] More recently, we showed in a preliminary study that camphor and norephedrine oxazoline *N*-oxide derivatives led to regio- and stereoselective cycloadditions with electron poor dipolarophiles.[10] This paper reports further cycloadditions with various dipolarophiles as well as a new oxidative-acidic cleavage of the adducts affording β-hydroxy ketones and allowing the recovery of the chiral inductor. The usefulness of this new asymmetric cycloaddition is further demonstrated by a short, convergent synthesis of a *Dacus oleae* fruit fly pheromone.[11,12]

Preparation of Starting Materials

Orthoester **6c** was synthesized from the known 4-(benzyloxy)-1-bromobutane[13] by sequential treatment with potassium cyanide in the presence of Aliquat 336,[14] hydrochloric acid in anhydrous methanol,[15] and anhydrous methanol in hexane.[16]

$R^1 - C(OMe)_3$

6a : R^1 = Me **6b** : R^1 = Pr **6c** : $R^1 = (CH_2)_4OBn$



7a : R^2 = CN; R^3 = H **7b** : $R^2 = CO_2Me$; R^3 = H

7c : $R^2 = CO_2Me$; R^3 = Me **7d** : $R^2 = CO_2Bn$; R^3 = Me

7e : $R^2 = CO_2Me$; R^3 = Pr **7f** : $R^2 = CO_2tBu$; R^3 = Pr

7g : $R^2 = SO_2Ph$; R^3 = Me **7h** : $R^2 = SO_2Ph$; R^3 = $(CH_2)_2OBn$

7i : R^2 = H ; $R^3 = (CH_2)_2OBn$.

Benzyl 2-butenoate (**7d**)[17] was prepared by esterification of crotonic acid according to Steglish.[18] Benzyl 2-hexenoate (**7e**)[17] was isolated after esterification of 2-hexenoic acid according to Kim[19] and *tert*-butyl-2-hexenoate (**7f**) by acidic treatment of the corresponding acid with isobutene.[20] 1-Propenyl phenyl sulfone (**7g**)[21] was obtained by transfer catalyst isomerization[22] of the commercially available 2-propenyl phenyl sulfone. Sulfone **7h** was prepared by a two-step sequence: nucleophilic substitution of 4-(benzyloxy)-1-bromobutane[14] afforded 4-(benzyloxy)butyl phenyl sulfone[23] which was in turn oxidized according to Julia[24] giving rise to 4-(benzyloxy)-1-butenyl sulfone (**7h**). 1-(Benzyloxy)-3-butene (**7i**)[25] was directly prepared from 4-(benzyloxy)-1-bromobutane by treatment with potassium *tert*-butoxide without solvent.[26]

Preparation of Oxazoline N-Oxides and Cycloadditions

Oxazoline *N*-oxides **9a–c** used in this study were prepared by a modification of the Coates method.[7] Thus, a mixture of trimethyl orthoesters **6a–c** and (+)-3-(hydroxyamino)borneol[27] (**8**) hydrochloride was heated at 40 °C in anhydrous dichloromethane or toluene in the presence of 4 Å molecular sieves as a methanol scavenger. The use of both trimethyl orthoesters and molecular sieves increased the rate of condensation and minimized the formation of byproducts due mainly to hydrolysis of the unstable oxazoline *N*-oxides. After completion of the reaction triethylamine and dipolarophile were added sequentially. The reaction medium was treated as indicated in Table 1, and cycloadditions were monitored by TLC (Scheme 3).

The results summarized in Table 1 deserve several comments. Yields for two steps, preparation of oxazoline

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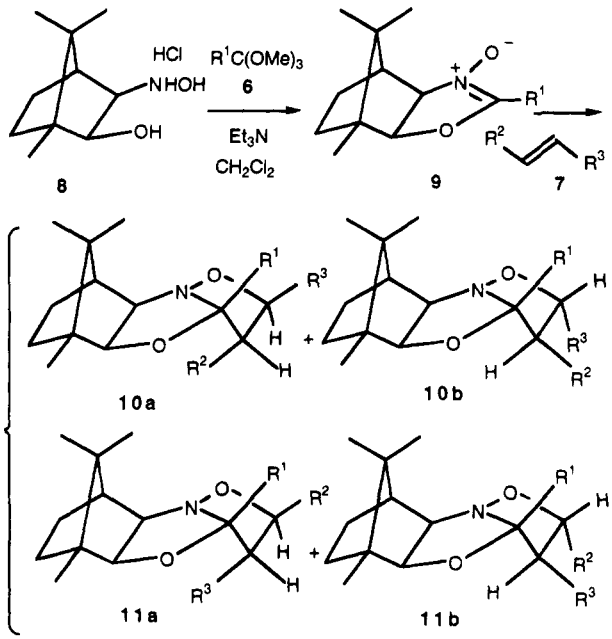
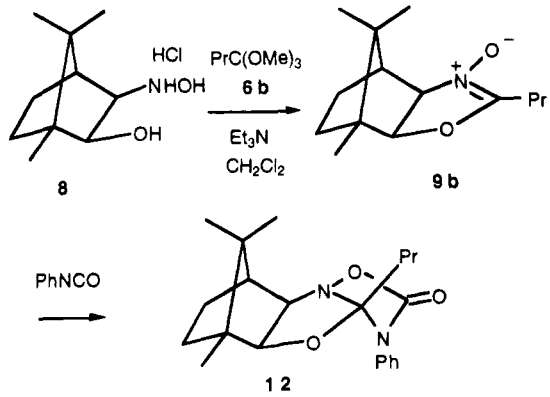
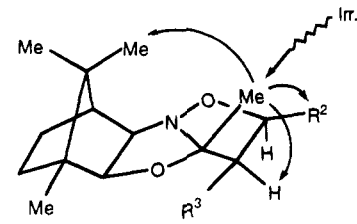
Scheme 3



Scheme 4



N-oxides and cycloadditions, were only moderate. Thus, three control experiments were undertaken in order to determine the limiting factor in this sequence of reactions. Treatment of oxazoline *N*-oxide **9b** with phenyl isocyanide afforded within 5 minutes at room temperature adduct **12** in 95% yield (Scheme 4). This yield decreased to 57% when *N*-oxide **9b** was heated at 80 °C in toluene for 2 h before cycloaddition. Finally *N*-oxide **9b** after refluxing for 5 days in dichloromethane afforded 3-(hydroxyamino)borneol propanoate. These results clearly demonstrated that yields of cycloadditions are limited by the thermic stability of oxazoline *N*-oxides and by their tendency to hydrolysis. The regio- and stereoselectivities were generally excellent except with acrylonitrile and methyl acrylate (entries 1 and 2) as already pointed out by Coates[7] with achiral oxazoline *N*-oxides. In all cases with other dipolarophiles, adducts **10a** were the only products isolated. The observed regioselectivity with 1,2 disubstituted olefins (entries 3–10) parallels the orientation of cycloadditions with nitrones and is more selective than in the case of nitrile oxides.[4c] However, with methyl acrylate and acrylonitrile (entries 1, 2) the regioselectivity is reversed with respect to nitrones. This peculiar orientation is probably due to an enhancement of the HOMO coefficient on oxygen in oxazoline *N*-oxides, the dipole HOMO/dipolarophile LUMO interaction being



10a1: R^3= CN; R^2= H
10a3: R^3= CO_2Me; R^2= Me

Figure 1.

still larger in this case. Comparison of experiments 5 and 6 showed the influence of temperature on the rate of cycloaddition. The versatility of these cycloadditions was also demonstrated by the use of various dipolarophiles. In addition, the reaction occurred as well, albeit in lower yield, with alkene devoid of electron-withdrawing groups (entries 11 and 13). Expectedly, these cycloadditions required longer reaction times. Furthermore, in contrast with cycloadditions with electron poor dipolarophiles which are always endoselective, the exo adducts were obtained with alkene **7i** (entries 11 and 13). The configurations of the newly created asymmetric centers in adducts **10a1** and **10a3** were determined after ^{1}H NMR NOE experiments (Figure 1) and were secured by an X-ray analysis of a single crystal of adduct **10a4**.[28] On the other hand, hydrogenolysis of the sulfone group in adduct **10a10** afforded a product identical in all respect with adduct **10a11**. Finally, the absolute configurations of adduct **10a13** has been confirmed after completion of the synthesis of a pheromone of *Dacus oleae* **23** (vide infra).

Hydrolysis of Adducts 10a. It is well established that isoxazolines or isoxazolidines resulting from cycloadditions of nitrile oxides or nitrones with dipolarophiles can be easily reduced, hydrogenolyzed, and hydrolyzed by many reagents affording β-hydroxy ketones or β-hydroxy amines.[4]

However, surprisingly, adducts **10a** proved to be stable under a variety of conditions either in acidic medium or under hydrogenolysis or both. In some cases, degradation products have been isolated. For instance, acidic hydrolysis of adduct **10a8** (TsOH, $C_6H_5CH_3$, H_2O, 80 °C, 24 h) afforded 5-nonen-4-one as the result of the hydrolysis of the *tert*-butyl ester followed by a decarboxylative elimination (Scheme 5).

In order to preclude this side reaction, adduct **10a8** was sequentially reduced with $LiAlH_4$, treated with TsCl–pyridine, and hydrogenolyzed affording compound **16**. Oxidation of **16** with *m*-CPBA afforded a transient *N*-oxide **17** which by a spontaneous elimination gave rise to the nitrone **18**. Acidic hydrolysis of **18** led to 3-(hydroxyimino)borneol (**19**) and to the β-hydroxy ketone **20**.[29] Relative configuration assignments were established by comparison of the chemical shift values with related β-hydroxycarbonyl compounds.[30] This method allowed both the isolation of the anticipated ketol **20** and the recovery of **19**, the direct precursor of 3-(hydroxyamino)-

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(29) The same procedure ((1) *m*-CPBA, (2) MeOH–HCl 0.5 N) has been applied directly to adduct **10a7**. A mixture of **19** and **14** was characterized by ^{1}H NMR, but **14** was the subject of a fast retroaldol reaction which precluded any purification.
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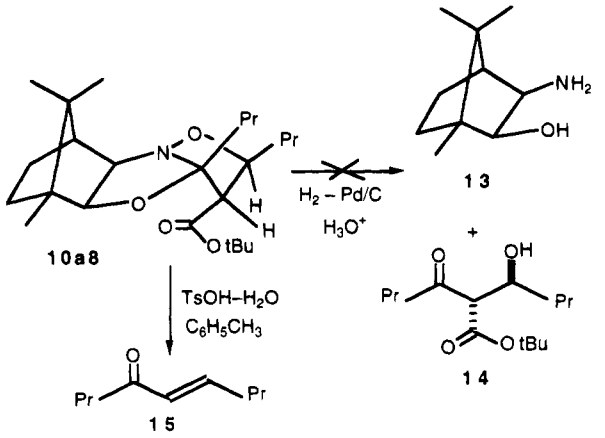
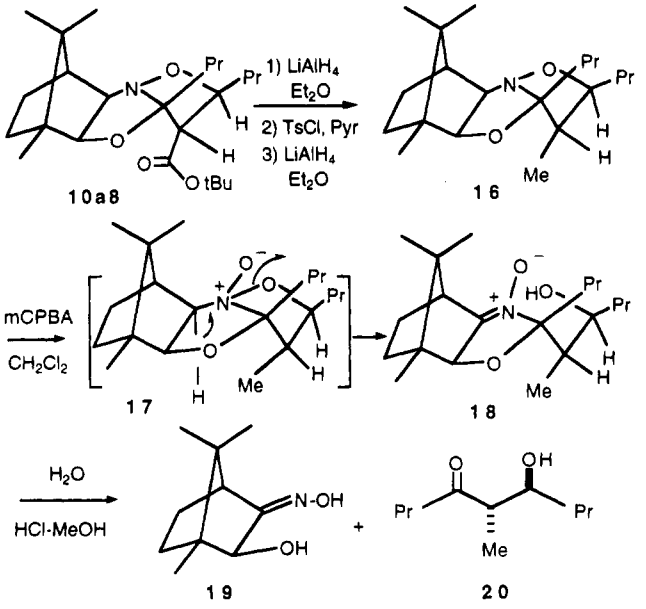
Scheme 5



Scheme 6

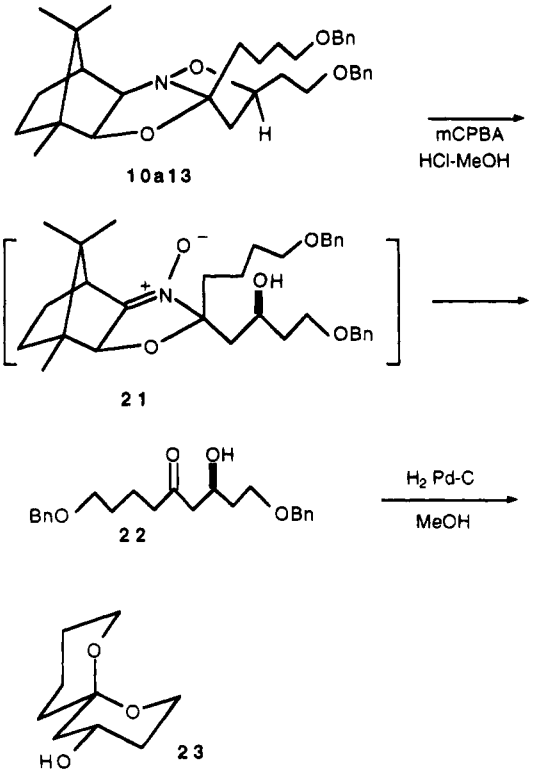


borneol (**8**)[27] (Scheme 6). Futhermore, the high overall yield of the transformation of **10a7** into **16** (85%) demonstrated the stability of these adducts, which contained masked alcohol and keto groups, during the manipulation of other functional groups.

Synthesis of 1,7-Dioxaspiro[5.5]undecan-4-ol (23). The title compound, one of the pheromones extracted from *Dacus oleae,* has been prepared by a short convergent synthesis as an illustration of the usefulness of this new asymmetric cycloaddition. Thus, a solution of adduct **10a13** in methanol–hydrochloric acid (0.5 N) has been oxidized with *m*-CPBA. After neutralization, ketol **22** was isolated in 84% yield. Hydrogenolysis of the benzyloxy groups with hydrogen in the presence of Pd–C afforded directly the anticipated spiroketalic pheromone **23** in 93% yield (Scheme 7).

In summary, cycloadditions of chiral oxazoline *N*-oxides with a wide variety of dipolarophiles afforded cycloadducts with a good regio- and stereoselectivity and in moderate yield. The resulting adducts can be subjected to functional group transformations before being oxidatively hydrolyzed in high yield affording β-hydroxy ketones and a direct precursor of the chiral inductor. Further uses of this new alternative to the asymmetric aldol condensation in the synthesis of natural products are being developed in our laboratory.

Scheme 7



Experimental Section

General. See ref 31.

5-(Benzyloxy)pentane nitrile.[32] To finely ground KCN (2.93 g, 45 mmol) were added water (0.81 g, 45 mmol), 4-(benzyloxy)-1-bromobutane (7.29 g, 30 mmol), and Aliquat 336 (0.33 g, 0.6 mmol). The mixture was shaken for 5 min with a mechanical stirrer and left for 4 h at 85 °C. Organic products were removed, after the addition of 50 mL of ether, by simple filtration through Florisil and purified by flash chromatography (pentane/ethyl acetate = 8/2) to afford 4.90 g (86%) of 5-(benzyloxy)pentanenitrile: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.35 (5H, m), 4.50 (2H, s), 3.50 (2H, t), 2.38 (2H, t), 1.78 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.5, 22.2, 28.2, 68.7, 72.5, 119.5, 127.3, 128.0, 138.0.

Methyl 5-(Benzyloxy)-1-pentanimidate Hydrochloride. 5-(Benzyloxy)pentanenitrile (3.78 g, 20 mmol), dry ether (10 mL), and dry methanol (0.79 mL, 22 mmol) were cooled at 0 °C with an ice bath. The solution was saturated with HCl, and the flask was stored at 0 °C for 2 d. Evaporation of the solvent afforded a white solid which was filtered, washed thoroughly with several portions of dry ether, and then dried to constant weight over solid potassium hydroxide in a desiccator evacuated at 15 mm (water aspirator) to afford 4.64 g (90%) of methyl 5-(benzyloxy)-1-pentanimidate hydrochloride as a fine white hygroscopic solid: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.35 (5H, m), 4.50 (2H, s), 4.25 (3H, s), 3.50 (2H, t), 2.80 (2H, t), 1.90–1.50 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.3, 28.5, 32.3, 60.4, 68.9, 72.7, 127.4, 128.1, 138.1, 180.0.

5-(Benzyloxy)-1,1,1-trimethoxypentane (6c). To methyl 5-(benzyloxy)-1-pentanimidate hydrochloride (5.15 g, 20 mmol) suspended in hexane (40 mL) was added dry methanol (2.42 mL, 60 mmol). The reaction mixture was stirred under argon for 48 h and then filtered to remove the precipitated ammonium chloride, and the filtrate was concentrated under reduced pressure to leave a slightly yellow liquid. This material was distilled over anhydrous potassium carbonate under reduced pressure to afford 4.02 g (75%) of 5-(benzyloxy)-

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1,1,1-trimethoxypentane (**6c**) as a colorless oil: bp 115 °C (0.3 mm); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35 (5H, m), 4.50 (2H, s), 3.48 (2H, t), 3.25 (9H, s), 1.80−1.40 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.4, 29.3, 29.9, 49.2, 70.0, 72.8, 115.6, 127.3, 128.2, 138.4.

1-Propenyl Phenyl Sulfone (7g).[21] To allyl phenyl sulfone (1.82 g, 10 mmol) in dichloromethane (10 mL) was added 5 mL of a 1 N aqueous NaOH solution and Bu_4NOH (0.26 g, 1 mmol). The mixture was stirred for 4 h at 25 °C, 40 mL of dichloromethane was added, and the organic layer was washed with 20 mL of water and 20 mL of a saturated aqueous NaCl solution, dried over $MgSO_4$, and filtered. After evaporation, 1.60 g (88%) of 1-propenyl phenyl sulfone (**7g**) was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.95−7.40 (5H, m), 6.95 (1H, m), 6.35 (1H, d), 1.90 (3H, d).

4-(Benzyloxy)butyl Phenyl Sulfone.[23] 4-(Benzyloxy)-1-bromobutane (8.0 g, 33 mmol) and sodium benzenesulfinate (5.4 g, 33 mmol) were stirred in DMF at 100 °C for 3 h. After cooling, the mixture was poured into 75 mL of a 5% aqueous $NaHCO_3$ solution and extracted with dichloromethane (2 × 100 mL). The organic layer was washed successively with a 5% aqueous $NaHCO_3$ solution (3 × 50 mL) and a saturated aqueous NaCl solution (50 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum to afford 7.5 g (75%) of 4-(benzyloxy)butyl phenyl sulfone as a white solid (mp = 64 °C): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.95−7.25 (10H, m), 4.45 (2H, s), 3.45 (2H, t), 3.15 (2H, t), 1.90−1.80 (2H, m), 1.75−1.65 (2H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.8, 27.9, 55.7, 68.9, 72.6, 127.3, 127.8, 128.1, 129.0, 133.4, 138.1, 138.9.

4-(Benzyloxy)-1-butenyl Phenyl Sulfone (7h). *n*-Butyllithium (3.1 mL, 5 mmol) was added at −78 °C to a solution of 4-(benzyloxy)butyl phenyl sulfone in THF (10 mL). After being stirred for 0.5 h at room temperature, the lithiated sulfone was added to a solution of the cupric acetate (2.41 g, 13.5 mmol) in 10 mL of THF at −78 °C. The mixture was stirred during 0.5 h at this temperature and hydrolyzed with a saturated solution of ammonium acetate. The residue was extracted with dichloromethane (25 mL) and the organic layer washed three times with ammonium acetate. The organic layer was dried over $MgSO_4$ and evaporated under vacuum. The crude product was analyzed by ^{1}H NMR as a 70/30 mixture of 4-(benzyloxy)-1-butenyl phenyl sulfone (**7h**) and 4-(benzyloxy)butyl phenyl sulfone and used without purification in cycloaddition reactions: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.95−7.10 (10H, m), 7.00 (1H, dt), 6.40 (1H, d), 4.50 (2H, s), 3.55 (2H, t), 2.50 (2H, m), 1.90−1.60 (4H, m).

1-(Benzyloxy)-3-butene (7i).[25] 4-(Benzyloxy)-1-bromobutane (2.43 g, 10 mmol) was added to finely ground *t*-BuOK (2.80 g, 25 mmol) and Aliquat 336 (202 mg, 0.5 mmol, 2% relative to the base). After being vigorously stirred for 10 min with a mechanical stirrer, the mixture was allowed to stand for 4 h at 25 °C. Filtration on Florisil (after addition of 50 mL of ether), evaporation of solvent, and distillation under vacuum afforded 1.21 g (75%) of 1-(benzyloxy)-3-butene (**7i**) as a colorless liquid: (bp = 53−55 °C/0.5 mm): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.35 (5H, s), 5.85 (1H, m), 5.05 (2H, m), 4.50 (2H, s), 3.55 (2H, t), 2.35 (2H, m).

Preparation of (+)-3-(Hydroxyamino)borneol (8). **8** was prepared according to Baldwin[27] and exhibits the following spectral data: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.41 (3H, brs, OH and NHOH), 3.73 (1H, d, J = 7.3), 3.25 (1H, d, J = 7.3), 1.83 (1H, d), 1.70−1.46 (4H, 2m), 1.04, 0.94, 0.78 (9H, 3s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.4, 21.5, 21.7, 27.3, 33.0, 46.6, 49.5, 49.6, 70.8, 79.9; $[\alpha]^{20}_D$ = +33.6° (c = 1.0, CH_2Cl_2). Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.82; H, 10.36; N, 7.56. Found: C, 64.69; H, 10.12; N, 7.33.

Typical Procedure for Cycloaddition Reactions. To a suspension of (+)-3-(hydroxyamino)borneol (**8**) hydrochloride (221.5 mg, 1 mmol) and 4 Å powdered molecular sieves (250 mg) in dichloromethane or toluene (2 mL) was added trimethylorthoester (1.2 mmol, 1.2 equiv). The mixture was stirred at 40 °C for 2 h, triethylamine (167 μL, 1.2 mmol) and dipolarophile (2 to 10 molar equiv) were added in succession, and the reaction medium was heated at the temperature and for the period indicated in Table 1. After cooling, filtration, and evaporation, the crude residue was dissolved in dichloromethane (10 mL), washed with water (5 mL) and a saturated aqueous NaCl solution (5 mL), dried over $MgSO_4$, and evaporated under vacuum. The crude product was purified by flash chromatography (silica gel Merck 60, 230−400 mesh).

Cycloaddition of 9a to 7a. Purification by flash chromatography (pentane/ether = 5/5) afforded an oil which was a 70:25:5 mixture of adducts **10a1**:**10b1**:(**11a1** or **11b1**) by NMR analysis. This oil was rechromatographed yielding pure **10a1** and a mixture of **10b1** and **11a1** (or **11b1**).

[3*S*-(3α,3a*β*,4aα,5*β*,8*β*,8aα)]-Octahydro-3a,5,10,10-tetramethyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-carbonitrile (10a1): ^{1}H NMR (C_6D_6, 200 MHz) δ 4.30 (1H, d, J = 8), 3.71 (1H, dd, J = 9, 9 Hz), 3.35 (1H, dd, J = 9, 9 Hz), 2.95 (1H, d, J = 8), 2.25 (1H, dd, J = 9, 9 Hz), 1.95 (1H, d, J = 4.5), 1.50−1.20 (4H, m), 1.30 (3H, s), 1.15, 0.95, 0.60 (9H, 3s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.5, 19.2, 22.3, 25.5, 26.8, 31.7, 42.6, 46.3, 48.3, 48.4, 68.4, 71.4, 89.3, 105.6, 116.3; MS (CI, NH_3) 263 (MH^+), 194; $[\alpha]^{20}_D$ = −88° (c = 0.7, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.42; H, 8.51; N, 10.52.

[3*R*-(3α,3aα,4a*β*,5α,8α,8a*β*)]-Octahydro-3a,5,10,10-tetramethyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-carbonitrile (10b1): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.30 (2H, 2dd, J = 9, 9 Hz), 3.98 (1H, d, J = 8), 3.75 (1H, d, J = 8), 3.22 (1H, dd, J = 9, 9 Hz), 2.05 (1H, d, J = 4.5), 1.68 (3H, s), 1.80−1.30 (4H, m), 1.05, 0.98, 0.86 (9H, 3s).

[2*S*-(2α,3a*β*,4aα,5*β*,8*β*,8aα)]-Octahydro-3a,5,10,10-tetramethyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazole-2-carbonitrile (11a1 or 11b1): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.60 (1H, dd, J = 9, 7 Hz), 4.12 (1H, dd, J = 9, 7 Hz), 4.00 (1H, d, J = 8), 3.45 (1H, dd, J = 9, 7 Hz), 3.10 (1H, d, J = 8), 2.05 (1H, d, J = 4.5), 1.77 (3H, s), 1.80−1.30 (4H,m), 1.08, 1.00, 0.85 (9H, 3s).

Cycloaddition of 9a to 7b. Purification by flash chromatography (pentane/ethyl acetate = 8/2) afforded **10a2** as an oil which was a 60:25:15 mixture of adducts **10a2**:**10b2**:(**11a2** or **11b2**) by NMR analysis. This oil was rechromatographed to afford pure **10a2** and a mixture of **10b2**, **11a2** and **11b2**.

[3*S*-(3α,3a*β*,4aα,5*β*,8*β*,8aα)]-Octahydro-3a,5,10,10-tetramethyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-carboxylic acid methyl ester (10a2): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.50 (1H, dd, J = 8, 8 Hz), 4.05 (1H, dd, J = 8, 7 Hz), 3.90 (1H, d, J = 6.5), 3.75 (3H, s), 3.30 (1H, d, J = 6.5), 3.15 (1H, dd, J = 8, 7 Hz), 2.10 (1H, d, J = 4), 1.70−1.30 (4H, m), 1.70 (3H, s), 1.00, 0.95, 0.80 (9H, 3s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.6, 19.3, 22.4, 25.7, 27.8, 32.0, 45.8, 48.2, 48.7, 52.1, 57.9, 67.4, 73.2, 89.6, 107.1, 170.3; MS (CI, NH_3) 296 (MH^+), 194; IR ($CHCl_3$) 2950, 2900, 1750; $[\alpha]^{20}_D$ = −64° (c = 0.96, $CHCl_3$). Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74. Found: C, 65.01; H, 8.28; N, 4.68.

[3*R*-(3α,3aα,4a*β*,5α,8α,8a*β*)]-Octahydro-3a,5,10,10-tetramethyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-carboxylic acid methyl ester (10b2): ^{1}H NMR($CDCl_3$, 250 MHz) δ 4.45 (1H, dd, J = 9, 9 Hz), 4.35 (1H, dd, J = 9, 7 Hz), 4.12 (1H, d, J = 8), 3.78 (3H, s), 3.50 (1H, dd, J = 9, 7 Hz), 3.15 (1H, d, J = 8), 2.05 (1H, d, J = 4.5), 1.48 (3H, s), 1.80−1.35 (4H, m), 1.05, 1.00, 0.82 (9H, 3s).

[2*S*-(2α,3a*β*,4aα,5*β*,8*β*,8aα)]-Octahydro-3a,5,10,10-tetramethyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazole-2-carboxylic acid methyl ester (11a2 or 11b2): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.95 (1H, dd, J = 10, 6 Hz), 3.95 (1H, d, J = 8), 3.76 (3H, s), 3.12 (1H, d, J = 8), 2.60 (1H, dd, J = 13, 10 Hz), 2.30 (1H, dd, J = 13, 6 Hz), 2.05 (1H, d, J = 4.5), 1.58 (3H, s), 1.80−1.30 (4H, m), 1.05, 0.98, 0.81 (9H, 3s).

[2*R*-(2α,3aα,4a*β*,5α,8α,8a*β*)]-Octahydro-3a,5,10,10-tetramethyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazole-2-carboxylic acid methyl ester (11b2 or 11a2): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.60 (1H, dd, J = 8, 6 Hz), 4.08 (1H, d, J = 8), 3.80 (3H, s), 3.58 (1H, d, J = 8), 2.55 (1H, dd, J = 9.5, 8 Hz), 2.30 (1H, dd, J = 9.5, 6 Hz), 2.05 (1H, d, J = 4.5), 1.58 (3H, s), 1.80−1.30 (4H, m), 1.08, 0.98, 0.82 (9H, 3s).

Cycloaddition of 9a to 7c. [2*S*-(2α,3*β*,3aα,4a*β*,5α,8α,-8a*β*)]-Octahydro-2,3a,5,10,10-pentamethyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-carboxylic Acid Methyl Ester (10a3). Purification by flash chromatography (pentane/ether = 7/3) afforded **10a3** (53%): ^{1}H NMR ($CDCl_3$,

250 MHz) δ 4.80 (1H, dt, *J* = 10, 6 Hz), 3.90 (1H, d, *J* = 8), 3.80 (3H, s), 3.40 (1H, d, *J* = 8), 2.70 (1H, d, *J* = 10), 2.10 (1H, d, *J* = 4.5), 1.80–1.30 (4H, m), 1.70 (3H, s), 1.25 (3H, d, *J* = 6), 1.00, 0.90, 0.75 (9H, 3s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.6, 17.6, 19.3, 22.4, 25.6, 27.9, 31.9, 45.7, 48.1, 48.7, 52.0, 65.1, 74.0, 74.9, 89.4, 107.5; MS (CI, NH_3) 309 (MH^+), 194; IR ($CHCl_3$) 2950, 1730; $[\alpha]^{20}_D = -63°$ (*c* = 1.17, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}NO_4$: C, 66.20; H, 8.49; N, 4.54. Found: C, 65.96; H, 8.70; N, 4.55.

Cycloaddition of 9a to 7d. [2*S*-(2α,3*β*,3aα,4a*β*,5α,8α,-8a*β*)]-Octahydro-2,3a,5,10,10-pentamethyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-carboxylic Acid Phenylmethyl Ester (10a4). Purification by flash chromatography (pentane/ether = 8/2) afforded **10a4** (52%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35 (5H, m), 5.05, 5.35 (2H, 2d, *J* = 11), 4.82 (1H, dt, *J* = 8.5, 5 Hz), 3.85 (1H, d, *J* = 7.5), 3.34 (1H, d, *J* = 7.5), 2.73 (1H, d, *J* = 8.5), 2.05 (1H, d, *J* = 4.5), 1.70 (3H, s), 1.30 (3H, d, *J* = 5), 1.25–1.80 (4H, m), 1.00, 0.85, 0.80, (9H, 3s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.5, 17.7, 19.3, 22.3, 25.6, 28.0, 31.7, 45.6, 48.1, 48.6, 65.1, 66.5, 74.0, 74.8, 89.1, 107.5, 127.8, 128.0, 135.7, 169.4; MS (CI, NH_3) 386 (MH^+), 210, 194; IR ($CHCl_3$) 2950, 1725; $[\alpha]^{20}_D = -112°$ (*c* = 1.03, $CHCl_3$). Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.47; H, 7.96; N, 3.67.

Cycloaddition of 9b to 7d. [2*S*-(2α,3*β*,3aα,4a*β*,5α,8α,-8a*β*)]-Octahydro-2,5,10,10-tetramethyl-3a-propyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-carboxylic Acid Phenylmethyl Ester (10a6). Purification by flash chromatography (pentane/ether = 8.5/1.5) afforded **10a6** (50%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35 (5H, m), 5.05, 5.38 (2H, 2d, *J* = 12.5), 4.87 (1H, dt, *J* = 9.5, 6 Hz), 3.85 (1H, d, *J* = 8), 3.34 (1H, d, *J* = 8), 2.89 (1H, d, *J* = 9.5), 2.06 (1H, d, *J* = 4.5), 1.97–1.35 (8H, m), 1.27 (3H, d, *J* = 6), 1.00, 0.84, 0.79 (9H, 3s), 0.92 (3H, t, *J* = 7); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.5, 14.3, 17.2, 17.7, 19.4, 22.4, 25.6, 31.8, 43.0, 45.6, 48.0, 48.6, 62.0, 66.5, 73.5, 75.2, 89.2, 109.4, 127.9, 128.0, 128.5, 135.5, 170.0; MS (CI, NH_3) 414 (MH^+), 222, 210, 194, 108; IR ($CHCl_3$) 2950, 1725; $[\alpha]^{20}_D = -90°$ (*c* = 1.05, $CHCl_3$). Anal. Calcd for $C_{25}H_{35}NO_4$: C, 72.61; H, 8.53; N, 3.38. Found: C, 72.57; H, 8.74; N, 3.47.

Cycloaddition of 9b to 7e. [2*S*-(2α,3*β*,3aα,4a*β*,5α,8α,-8a*β*)]-Octahydro-5,10,10-trimethyl-2,3a-dipropyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-carboxylic Acid Methyl Ester (10a7). Purification by flash chromatography (pentane/ether = 9/1) afforded **10a7** (63%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.75 (1H, dt, *J* = 9.5, 5.5 Hz), 3.95 (1H, d, *J* = 8), 3.75 (3H, s), 3.35 (1H, d, *J* = 8), 2.87 (1H, d, *J* = 9.5), 2.05 (1H, d, *J* = 4), 2.00–1.10 (12H, m), 0.95, 0.91 (6H, 2t), 1.00, 0.88, 0.79 (9H, 3s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.6, 14.1, 14.4, 17.2, 19.1, 19.4, 22.5, 25.6, 32.0, 35.0, 43.0, 45.7, 48.1, 48.6, 52.1, 60.7, 73.6, 79.1, 89.4, 109.0, 170.8; MS (CI, NH_3) 366 (MH^+); IR ($CHCl_3$) 2950, 1725; $[\alpha]^{20}_D = -41°$ (*c* = 0.64, $CHCl_3$). Anal. Calcd for $C_{21}H_{35}NO_4$: C, 69.00; H, 9.65; N, 3.83. Found: C, 68.95; H, 9.65; N, 3.83.

Cycloaddition of 9b to 7f. [2*S*-(2α,3*β*,3aα,4a*β*,5α,8α,-8a*β*)]-Octahydro-5,10,10-trimethyl-2,3a-dipropyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazole-3-carboxylic Acid 1,1-Dimethylethyl Ester (10a8). Purification by flash chromatography (pentane/ether = 9/1) afforded **10a8** (53%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.71 (1H, dt, *J* = 8.5, 4 Hz), 3.92 (1H, d, *J* = 6), 3.35 (1H, d, *J* = 6), 2.75 (1H, d, *J* = 8.5), 2.05 (1H, d, *J* = 4.5), 2.00–1.20 (10H, m), 1.47 (9H, s), 0.95, 0.90 (6H, 2t, *J* = 6), 1.00, 0.85, 0.80 (9H, 3s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.4, 14.1, 14.5, 17.2, 19.1, 19.4, 22.4, 25.7, 28.0, 31.0, 35.1, 43.1, 45.7, 48.0, 48.7, 61.1, 73.5, 78.7, 81.1, 89.1, 109.0, 169.5; MS (CI, NH_3) 408 (MH^+), 222, 204, 148; IR ($CHCl_3$) 2950, 1725; $[\alpha]^{20}_D = -53°$ (*c* = 1.31, $CHCl_3$). Anal. Calcd for $C_{24}H_{41}NO_4$: C, 70.72; H, 10.14; N, 3.44. Found: C, 70.58; H, 10.06; N, 3.63.

Cycloaddition of 9a to 7g. [2*S*-(2α,3*β*,3aα,4a*β*,5α,8α,-8a*β*)]-Octahydro-2,3a,5,10,10-pentamethyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazol-3-yl Phenyl Sulfone (10a9). Purification by flash chromatography (pentane/ether = 5/5) afforded **10a9** (42%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.00–7.40 (5H, m), 4.85 (1H, dt, *J* = 8, 5.5 Hz), 4.48 (1H, d, *J* = 6.5), 3.35 (1H, d, *J* = 6.5), 3.18 (1H, d, *J* = 8), 2.05 (1H, d, *J* = 4.5), 1.80–1.30 (4H, m), 1.35 (3H, d, *J* = 5.5), 1.25 (3H, s), 0.95, 0.90, 0.80 (9H, 3s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.4, 18.6, 19.2, 22.4, 25.5, 28.4, 31.8, 45.5, 48.1, 48.7, 72.9, 73.9, 80.4, 89.7, 105.1, 128.4, 128.8, 129.1, 134.0; MS (CI, NH_3) 392 (MH^+), 200, 194; IR ($CHCl_3$) 2950, 1150; $[\alpha]^{20}_D = -160°$ (*c* = 0.8, $CHCl_3$). Anal. Calcd for $C_{21}H_{29}NO_4S$: C, 64.42; H, 7.46; N, 3.56; S, 8.19. Found: C, 64.33; H, 7.48; N, 3.55; S, 8.43.

Cycloaddition of 9a to 7h. [2*S*-(2α,3*β*,3aα,4a*β*,5α,8α,-8a*β*)]-Octahydro-2-[2-(benzyloxy)ethyl]-3a,5,10,10-tetramethyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazol-3-yl Phenyl Sulfone (10a10). Purification by flash chromatography (pentane/ether = 5/5) afforded **10a10** (30%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.90–7.30 (10H, m), 4.90 (1H, dt, *J* = 8, 4 Hz), 4.50 (3H, d + s, *J* = 8), 3.70 (1H, d, *J* = 8), 3.55 (2H, t, *J* = 4.5), 3.25 (1H, d, *J* = 8), 2.05 (1H, d, *J* = 4.5), 1.95–1.30 (6H, m), 1.20 (3H, s), 0.95, 0.90, 0.80 (9H, 3s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.4, 19.3, 22.4, 25.5, 28.3, 32.0, 32.4, 46.1, 47.8, 48.8, 65.9, 72.8, 73.8, 74.0, 77.9, 89.8, 127.6, 127.9, 128.4, 128.8, 129.2, 133.9; MS (CI, NH_3) 513 (MH^+), 194; $[\alpha]^{20}_D = -112°$ (*c* = 0.98, $CHCl_3$).

Cycloaddition of 9a to 7i. [2*S*-(2α,3*β*,3aα,4a*β*,5α,8α,-8a*β*)]-Octahydro-2-[2-benzyloxy)ethyl]-3a,5,10,10-tetramethyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazole (10a11). Purification by flash chromatography (pentane/ether = 7.5/2.5) afforded **10a11** (50%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.35 (5H, m), 4.60 (1H, ddt, *J* = 9.5, 7, 4 Hz), 4.48 (2H, s), 3.95 (1H, d, *J* = 8), 3.55 (2H, t, *J* = 7), 3.18 (1H, d, *J* = 8), 2.40 (1H, dd, *J* = 13.5, 9.5 Hz), 2.05 (1H, d, *J* = 4.5), 1.95–1.35 (7H, m), 1.55 (3H, s), 1.05, 0.95, 0.80 (9H, 3s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.7, 19.5, 22.4, 25.6, 26.3, 32.1, 35.3, 44.0, 46.1, 47.8, 48.4, 67.1, 72.5, 73.0, 74.9, 87.2, 104.4, 127.6, 128.3; MS (CI, NH_3) 372 (MH^+); IR ($CHCl_3$) 2950; $[\alpha]^{20}_D = -46°$ (*c* = 1.23, $CHCl_3$).

Cycloaddition of 9c to 7h. [2*S*-(2α,3*β*,3aα,4a*β*,5α,8α,-8a*β*)]-Octahydro-2-[2-(benzyloxy)ethyl]-3a-[4-(benzyloxy)butyl]-5,10,10-trimethyl-5,8-methano-2*H*-isoxazolo-[3,2-*b*]benzoxazol-3-yl Phenyl Sulfone (10a12). Purification by flash chromatography (pentane/ether = 5/5) afforded **10a12** (25%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.90–7.25 (15H, m), 4.95 (1H, dt, *J* = 9.5, 3 Hz), 4.55 (1H, d, *J* = 8), 4.45 (2H, s), 4.40 (2H, s), 3.80 (1H, d, *J* = 9.5), 3.70–3.45 (2H, m), 3.25 (3H, d + s, *J* = 8), 2.05 (1H, d, *J* = 4.5), 2.00–1.10 (12H, m), 0.98, 0.95, 0.80 (9H, 3s).

Cycloaddition of 9c to 7i. [2*S*-(2α,3*β*,3aα,4a*β*,5α,8α,-8a*β*)]-Octahydro-2-[2-(benzyloxy)ethyl]-3a-[4-(benzyloxy)butyl]-5,10,10-trimethyl-5,8-methano-2*H*-isoxazolo-[3,2-*b*]benzoxazole (10a13). Purification by flash chromatography (pentane/ethyl acetate = 8.5/1.5) afforded **10a13** (23%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.35 (10H, m), 4.55 (1H, ddt, *J* = 9.4, 7, 3 Hz), 4.45 (4H, s), 3.90 (1H, d, *J* = 9.5), 3.55 (2H, t, *J* = 6), 3.48 (2H, t, *J* = 6), 3.15 (1H, d, *J* = 9.5), 2.20 (1H, dd, *J* = 14, 9.4 Hz), 2.05 (1H, d, *J* = 4.5), 2.00–1.10 (13H, m), 1.05, 0.95, 0.80 (9H, 3s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.6, 19.6, 21.1, 22.4, 25.8, 30.0, 32.0, 34.9, 39.2, 41.2, 46.1, 47.8, 48.4, 67.1, 70.1, 72.7, 72.9, 73.0, 74.7, 87.0, 106.7, 127.4, 127.6, 128.3; MS (CI, NH_3) 520 (MH^+), 194; $[\alpha]^{20}_D = -24°$ (c = 1.23, $CHCl_3$). Anal. Calcd for $C_{33}H_{45}NO_4$: C, 76.26; H, 8.73; N, 2.69. Found: C, 75.97; H, 8.67; N, 2.80.

Preparation of *β*-hydroxy ketone 20. [2*S*-(2α,3*β*,3aα,-4a*β*,5α,8α,8a*β*)]-Octahydro-5,10,10-trimethyl-2,3a-dipropyl-3-(hydroxymethyl)-5,8-methano-2*H*-isoxazolo[3,2-*b*]-benzoxazole (Reduction of Adduct 10a8). To a suspension of $LiAlH_4$ (76 mg, 2 mmol) in anhydrous ether (10 mL) was slowly added **10a8** (407 mg, 1 mmol) in solution in ether (2 mL) at room temperature under argon, and the mixture was stirred for 4 h. A saturated NH_4Cl solution (5 mL) was added, the aqueous layer was extracted with 10 mL of ether, and the combined extracts were washed with a saturated aqueous NaCl solution (2 × 5 mL), dried over $MgSO_4$, filtered, and evaporated to yield 323 mg (96%) of a colorless oil which was used in the following step without purification: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.94 (1H, d, *J* = 7.8), 3.95 (1H, dd, *J* = 9.5, 2 Hz), 3.85 (1H, dd, *J* = 9.5, 7.5 Hz), 3.65 (1H, dt, *J* = 6, 3 Hz), 3.25 (1H, d, *J* = 7.8), 2.35 (1H, ddd, *J* = 7.5, 6, 2 Hz), 2.05 (1H, d, *J* = 4.5), 2.00–1.25 (12H, m), 1.05, 0.93, 0.80 (9H, 3s), 0.93, 0.92 (6H, 2t); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.5, 14.1,

14.5, 17.2, 19.1, 19.4, 22.5, 25.6, 32.4, 35.8, 43.3, 45.2, 48.5, 48.7, 56.6, 62.4, 73.7, 79.7, 90.2, 107.5; $[\alpha]^{20}_D = -76°$ (c =1.05, $CHCl_3$). Anal. Calcd for $C_{20}H_{35}NO_3$: C, 71.60; H, 9.91; N, 4.17. Found: C, 71.21; H, 9.80; N, 3.98.

Tosylation. Alcohol (207 mg, 0.61 mmol) and tosyl chloride (235 mg, 1.22 mmol) were stirred in pyridine (5 mL) at 25 °C for 24 h. Ether (30 mL) and water (15 mL) were added, the aqueous layer was extracted with ether (2 × 20 mL), and the organic layer was washed with a 1 N HCl aqueous solution (2 × 20 mL) and water (20 mL), dried over $MgSO_4$, and evaporated to afford 278 mg (93%) of an oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.80 (2H, d, J = 7.8), 7.40 (2H, d, J = 7.8), 4.25 (1H, dd, J = 10, 4.5 Hz), 4.05 (1H, dd, J = 10, 10 Hz), 4.00 (1H, dt, J = 9, 3 Hz), 3.55 (1H, d, J = 7.8), 3.15 (1H, d, J = 7.8), 2.45 (3H, s), 2.20 (1H, ddd, J = 10, 9, 4.5 Hz), 2.05 (1H, d, J = 4.5), 1.85−1.20 (12H, m), 1.00, 0.87, 0.79 (9H, 3s), 0.89, 0.85 (6H, 2t); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.5, 14.1, 17.1, 18.9, 19.3, 21.6, 22.4, 25.6, 32.1, 35.5, 42.7, 45.5, 48.5, 48.6, 53.4, 69.0, 73.8, 76.4, 81.4, 89.6, 107.2, 127.9, 132.9, 145.0; $[\alpha]^{20}_D = -84°$ (c = 0.72, $CHCl_3$). Anal. Calcd for $C_{27}H_{41}NO_5S$: C, 65.96; H, 8.41; N, 2.85; S, 6.52. Found: C, 65.95; H, 8.40; N, 2.69; S, 6.29.

[2*S*-(2α,3β,3aα,4aβ,5α,8α,8aβ)]-Octahydro-3,5,10,10-tetramethyl-2,3a-dipropyl-5,8-methano-2*H*-isoxazolo[3,2-*b*]benzoxazole (16) (Hydrogenolysis of the Tosylate). To a suspension of $LiAlH_4$ (38 mg, 1 mmol) in anhydrous ether (5 mL) was added tosylate (260 mg, 0.53 mmol) at 20 °C under argon, and the mixture was stirred for 5 h. Five mL of a saturated NH_4Cl solution was added, the aqueous layer was extracted twice with 10 mL of ether, and the combined extracts were washed with a saturated aqueous NaCl solution (2 × 5 mL), dried over $MgSO_4$, filtered, and evaporated to yield 162 mg (95%) of **16** as a colorless oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 3.75 (1H, dt, J = 10, 4.5 Hz), 3.72 (1H, d, J = 7), 3.20 (1H, d, J = 7), 2.05 (1H, d, J = 4.5), 1.95−1.30 (12H, m), 1.00 (3H, d, J = 7), 1.08, 0.95, 0.80 (9H, 3s), 0.92, 0.90 (6H, 2t); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.7, 12.5, 14.3, 14.6, 17.5, 19.2, 19.5, 22.5, 25.9, 32.2, 35.2, 43.0, 45.5, 48.4, 48.8, 49.5, 74.2, 83.5, 89.1, 108.0; $[\alpha]^{20}_D = -92°$ (c = 1.05, $CHCl_3$); Anal. Calcd for $C_{20}H_{35}NO_2$: C, 74.72; H, 10.97; N, 4.36. Found: C, 74.69; H, 10.97; N, 4.06.

Oxidation of 16: Preparation of Nitrone 18. To a solution of **16** (69 mg, 0.21 mmol) in dichloromethane (5 mL), was added *m*-CPBA (40 mg, 0.23 mmol). The mixture was stirred for 1 h, and then dichloromethane (5 mL) was added. The organic layer was washed with a 5% $NaHCO_3$ solution (3 × 5 mL), dried over $MgSO_4$, and evaporated to yield 65 mg (92%) of nitrone **18** as an oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 4.05 (1H, s), 3.55 (1H, m), 1.95 (1H, d, J = 4.5), 1.90−1.30 (9H, m), 1.25 (3H, d, J = 7), 1.05−0.80 (15H, m).

(5*S*,6*S*)-6-Hydroxy-5-methylnonan-4-one (20) (Hydrolysis of Nitrone 18). Nitrone **18** (65 mg, 0.19 mmol) was stirred in a 4:1 MeOH/0.5 N HCl solution (2.5 mL) for 2 h. Methanol was evaporated, dichloromethane (10 mL) was added, and the organic layer was washed with water (2 × 5 mL), dried over $MgSO_4$, and evaporated. Purification by thin layer chromatography yielded 27 mg (82%) of **20** and 24 mg (70%) of 3-(hydroxyimino)borneol (**19**): ^1H NMR ($CDCl_3$, 200 MHz) δ 3.70 (1H, m), 2.65 (1H, dd, J = 10, 5.5 Hz), 2.60−2.35 (2H, 2dt, J = 7.8, 5.5 Hz), 1.60 (2H, m), 1.60−1.30 (4H, m), 1.10 (3H, d, J = 5.5), 0.95 (6H, 2t, J = 5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.7, 14.0, 14.1, 16.8, 18.8, 36.9, 44.8, 51.2, 73.4, 200.4; $[\alpha]^{20}_D = -25°$ (c = 0.45, $CHCl_3$).

(3*S*)-1,9-Bis(benzyloxy)-3-hydroxynonan-5-one (22). **10a13** (52 mg, 0.1 mmol) was dissolved in a 4:1 mixture of methanol/0.1 N HCl (2.5 mL), and *m*-CPBA (19 mg, 0.11 mmol) was added. After 12 h, methanol was evaporated, dichloromethane (10 mL) was added, and the organic layer was washed with a 5% aqueous $NaHCO_3$ solution (3 × 5 mL) and saturated aqueous NaCl solution (5 mL), dried over $MgSO_4$, filtered, and evaporated. Purification by thin layer chromatography (ether/pentane 7:3) afforded 31 mg (84%) of **22** as a colorless oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.35 (10H, m), 4.52 (2H, s), 4.48 (2H, s), 4.25 (1H, tt, J = 5.6), 3.67 (2H, dt, J = 5.5, 2.3 Hz), 3.45 (2H, t, J = 5.5), 2.55 (2H, d, J = 5.6), 2.45 (2H, t, J = 5), 1.90−1.50 (4H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.3, 29.1, 36.1, 43.3, 49.2, 66.5, 67.9, 69.9, 72.9, 73.2, 127.5, 127.6, 127.7, 128.3, 128.4, 138.0, 138.5, 200.9; $[\alpha]^{20}_D = +13.7$ (c = 1.28, $CHCl_3$).

(4*S*,6*S*)-1,7-Dioxaspiro[5.5]undecan-4-ol (23). β-Hydroxy ketone **22** (25 mg, 67 μmol) was dissolved in methanol (2 mL) and stirred under hydrogen atmosphere in the presence of a catalytic amount of 10% palladium on activated carbon for 1 h. Filtration on Celite and evaporation of the solvent afforded 10.7 mg (93%) of 1,7-dioxaspiro[5.5]undecan-4-ol (**23**): ^1H NMR ($CDCl_3$, 250 MHz) δ 4.08 (1H, tt, J = 11, 5 Hz), 3.75−3.50 (4H, m), 2.01 (1H, ddd, J = 11, 5.5, 2 Hz), 1.96 (1H, ddd, J = 12.5, 5, 2 Hz), 1.89 (1H, ddd, J = 12, 5, 2 Hz), 1.81 (1H, tt, J = 12, 5 Hz), 1.68−1.44 (6H, m), 1.29 (1H, dd, J = 11.5, 11 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.5, 25.1, 35.1, 35.5, 45.2, 58.8, 60.4, 64.4, 97.2; $[\alpha]^{20}_D = +116°$ (c = 0.60, pentane) (lit.[12a] $[\alpha]^{20}_D = +120°$ (c = 2.61, pentane)).

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Supplementary Material Available: Preparations of compounds **7d−f** and copies of ^1H and ^{13}C NMR spectra of **10a8**, **12**, **20**, **22**, and **23** (10 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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