Diastereoselective Conjugate Addition to (+)-Camphorsulfonic Acid Derived Nitroalkenes: Synthesis of α-Hydroxy and α-Amino Acids

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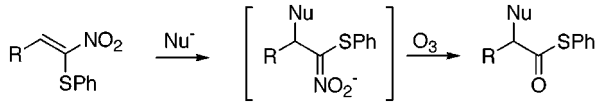
Diastereoselective tandem conjugate addition of both oxygen- and nitrogen-centered nucleophiles to the novel (1*S*)-10-camphorsulfonic acid derived nitroalkenes **9**, **10**, and **11** and ozonolysis gave the α-hydroxy and α-amino thiol acid derivatives **12**, **13**, and **14**. In all cases, the (*R*)-diastereomer was formed as the major component albeit with only modest levels of selectivity (33−71% de). The structures of the products and the stereochemistry of the Michael addition step were unequivocally established by X-ray crystallographic studies of nitroalkenes **9** and **10** and (2*S*)-**12c** and (2*R*)-**13a** and by alternative syntheses from (*S*)-alanine, (*S*)-valine, and ethyl (*S*)-lactate.

Introduction

1-(Phenylthio)-1-nitroalkenes **1** are useful intermediates for the elaboration of α-substituted phenylthioesters **3** by the Michael addition of oxygen-, nitrogen-, and carbon-centered nucleophiles followed by in situ ozonolysis of nitronate intermediates **2** (Scheme 1).[1] 1-(Benzyloxy)-1-nitroalkenes show comparable reactivity. These methods have been applied for the synthesis of nikkomycin B,[2] bicyclic β-lactams,[3] and 6-aminopenicillanic acid.[4] The availability of both enantiomers of camphor-10-sulfonic acid as inexpensive bulk chemicals has been exploited by Oppolzer in the development of a number of practical chiral auxiliaries.[5] These auxiliaries confer good to excellent π-facial topological differentiation to reaction of their enoyl as well as to their enolate derivatives and have been exploited for such diverse transformations as Diels−Alder reactions,[6] 1,4-additions of organocopper reagents,[7] electrophilic halogenation[8] (and hence α-amino acids by S_N2 displacement with azide as nucleophile[9]), and electrophilic amination reactions.[10] We now report the use of a novel (+)-camphor-10-sulfonic acid derived auxiliary to effect diastereoselective conjugate additions to pendant nitroalkene moieties. In situ ozonolysis of the intermediate nitronate anion gave rise directly to protected α-hydroxy and α-amino acids in moderate to good yield and diastereomeric excess.

Scheme 1



1 **2** **3**

Results and Discussion

Thionation of the camphor derivative **4**[6a] with Lawesson's reagent in toluene at reflux gave thione **5** (82%) and this was directly reduced with sodium borohydride to provide thiol **6** as a colorless crystalline single diastereomer in excellent yield (Scheme 2). In conversion of thiol **6** to nitromethyl sulfide **8**, temperature control was found to be critical. Addition of 1 equiv of sulfuryl choride to thiol **6** at 0 °C or −20 °C or by slow warming from −78 °C resulted in the formation of significant quantities (20−40%) of bornyl chloride. Slow addition of sulfuryl chloride to thiol **6** at −40 °C, however, provided **7** of ca. 95% purity as estimated from its ^{1}H NMR spectrum, and this was used without further purification. Disappointingly, the action of sodium nitromethylate, freshly prepared from sodium ethoxide and nitromethane, on sulfenyl chloride **7** produced **8** in only 15% yield. However, the use of *n*-butyllithium to deprotonate nitromethane followed by the addition of the resulting slurry to **7** in THF furnished **8** in a reproducible 50% overall yield from **6**. Nitroalkane **8** was converted into the substituted nitroalkenes **9**, **10**, and **11** all exclusively as *Z*-isomers by condensation with the appropriate aldehydes in the presence of piperidinium acetate.[11]

Three representative nucleophiles (potassium phthalimide, potassium toluene-4-sulfonamide, and sodium methoxide) were examined to assay the levels of diastereoselectivity imparted on conjugate additions to chiral nitroalkenes **9**−**11** (Table 1). For the addition of potassium phthalimide to **10**, DMF was found to be the preferred solvent, the nitroalkene being completely consumed within 1 h at 0 °C. In situ ozonolysis at −78 °C gave the thioester **13a** (60%) with a 33% de (Table 1, entry 1) in favor of the (2*R*) epimer (vide infra). The

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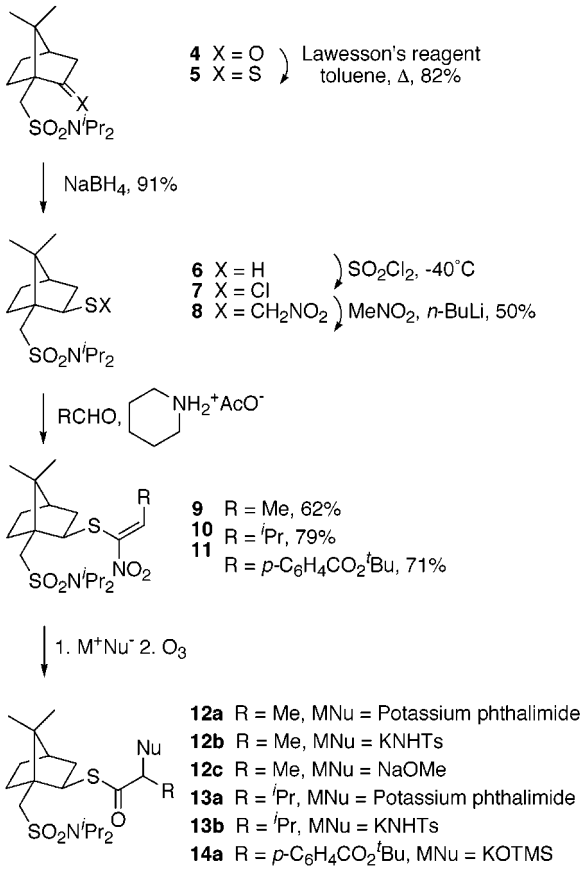
Scheme 2



diastereoselectivity could be improved to 43% de, (2*R*) major, by performing the initial conjugate addition at −20 °C (entry 2). However, solubility factors prevented any further temperature decreases. Accordingly, mixed solvent systems were examined, and it was found that a 1:1 mixture of DMF and dichloromethane allowed the conjugate addition to proceed smoothly at −40 °C with a corresponding increase in de (71%) (entry 3).

The other nucleophiles examined were also found to add with moderate to good levels of diastereoselectivity to chiral nitroalkenes **9** and **10** (entries 5−8). For the addition of potassium phthalimide to **9** (entry 4), a 1:1 mixture of epimers was isolated where a fast epimerization is presumably responsible for this anomalous result. Conjugated nitroalkene **11** was found to be resistant to attack by both nitrogen-centered nucleophiles, potassium phthalimide and potassium toluene-4-sulfonamide, as well as sodium methoxide, consistent with the poor reactivity previously encountered with 2-aryl-1-(phenylthio)nitroalkenes.[12] The presumably more reactive potassium trimethylsilanolate was found to add, generating adduct **14a** in 74% yield (entry 9) after ozonolysis.

In all the above cases the 2*R*-epimer resulting from nucleophilic attack from the Cα-*re* face of the nitroalkene predominated, albeit with modest diastereoselectivity. This was unequivocably demonstrated by a combination of single-crystal X-ray analyses and by preparation of thioesters of known absolute configuration and correlation with the diastereomeric product mixtures. Thus, single crystals of the major diastereomer of **13a** were available for X-ray analysis after two recrystallizations from hexanes, and this proved to be the 2*R* epimer. Authentic samples of diastereomerically pure 2*S*-epimers of *N*-tosyl derivatives **12b** and **13b** were available from *S*-alanine and *S*-valine, respectively, by 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI) coupling[13] of *N*-tosyl-protected amino acids[14] with thiol **6**. Similarly, coupling of thiol **6** with carboxylic acid **17** available from (*S*)-ethyl lactate **15** via silver oxide mediated methylation and subsequent hydrolysis of the resulting α-methoxy ester **16** (Scheme 3) furnished (2*S*)-**12c** as a single diastereoisomer. In each case the authentic 2*S* epimer proved to be identical to the minor diastereomeric component from the tandem conjugate addition−ozonolysis thereby confirming the preference for *re* face attack. It is pertinent to compare our findings with the results of related work by Oppolzer using similar auxiliaries where the diastereoselectivities are generally excellent. In Oppolzer's studies there are two key features that rationalize the observed π-facial discrimination.[5,15] For substrates such as silyl ketene acetal **18**[16] the C7′−C1′−C10′−S′ torsion angle is close to 180°, and as a result of sulfonamide conjugation the lone pair on nitrogen bisects the O−S′−O angle. Additionally, there is a *syn*-periplanar disposition of the C1−OSi and C2′−H bonds which places a cyclohexyl ring firmly on top and thus shielding the Cα-*re* face of the olefinic double bond (Figure 1). The X-ray crystal structures of **9** and **10** show that these nitroalkenes also exhibit an *anti*-periplanar disposition of the C10′−S′ and C1′−C7′ bonds with the lone pair of nitrogen bisecting the O−S′−O angle. However, the C1−NO_2 bond is rotated by 118° in **9** and 108° in **10** with respect to the C2′−H bond about the C1···C2′ vector thus resulting in less than perfect shielding of the Cα-*si* face of the nitroalkene. It seems likely that this stems from unfavorable stereoelectronic interactions between the nitro group and the sulfonyl group, and it is reasonable to speculate that this unfavorable solid-state interaction translates to the solution phase also. This may go part-way in explaining the unexpected moderate levels of diastereoselectivity imparted by the auxiliary in these systems. In any case, it is apparent from the results obtained, that in the reactive conformation of the molecule, the Cα-*re* face of the nitroalkene is the less shielded, giving rise to a predominance of the 2*R*-epimer in the diastereoisomeric product mixtures.

Experimental Section

General Procedures. All reactions were carried out under a dry argon or nitrogen atmosphere at ambient temperature unless otherwise stated. Column chromatography was carried out on E. Merck or BDH silica gel 60, 230−400 mesh ASTM using flash chromatography techniques.[17] Analytical thin-layer chromatography (TLC) was performed on E. Merck precoated silica gel 60F_{254} plates. Hexanes, CH_2Cl_2, EtOAc, and Et_2O as eluants were ACS reagent grade solvent or GPR grade from BDH and undistilled. The following reaction solvents were purified by distillation: MeOH (from Mg, I_2), DMF (from alumina), *t*-BuOH (from CaH_2), CH_2Cl_2 (from

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Table 1. Conjugate Diastereoselective Addition of Nucleophiles to Chiral Nitroalkenes

entry	nitroalkene	nucleophile[a]	solvent	T (°C)[a,b]	product	yield (%)[c]	de (%)[d]
1	**10**	KPht	DMF	0	**13a**	60	33
2	**10**	KPht	DMF	−20	**13a**	58	43
3	**10**	KPht	1:1 DMF:CH_2Cl_2	−40	**13a**	61	71
4	**9**	KPht	1:1 DMF:CH_2Cl_2	−45	**12a**	65	0
5	**10**	KNHTs	DMF	0	**13b**	60	52
6	**10**	KNHTs	1:1 DMF:CH_2Cl_2	0	**13b**	71	50
7	**9**	KNHTs	1:1 DMF:CH_2Cl_2	0	**12b**	72	33
8	**9**	NaOMe	1:1 DMF:CH_2Cl_2	−35	**12c**	32	51
9	**11**	KOTMS	1:1 DMF:CH_2Cl_2	−20	**14a**	74[e]	40

[a] Temperature at which conjugate addition performed. All ozonolyses were performed at −78 °C. [b] With the exception of entry 1, all given temperatures are the minimum at which the solution remained homogeneous. [c] Isolated yield after chromatography. [d] Determined by integration of the relevant diastereomeric resonances in the ^{1}H NMR spectrum. [e] Isolated as the free alcohol by direct cleavage of the TMS adduct with 10% methanolic citric acid.

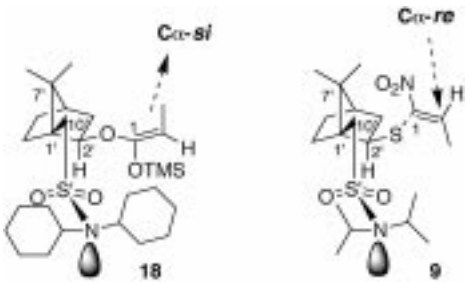
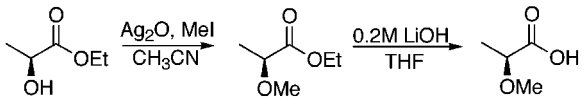


Figure 1.

Scheme 3



CaH_2), Et_2O (from Ph_2CO−Na) and THF (from Ph_2CO−K). Commercial samples of *n*-butyllithium were titrated against freshly recrystallized diphenylacetic acid.[18] Powdered molecular sieves were activated by drying at 120 °C for 24 h.

N,*N*-Diisopropyl-(1*S*)-10-camphorsulfonamide **4**[6a] was prepared from (1*S*)-(+)-camphorsulfonic acid via (1*S*)-10-camphorsulfonyl chloride.[19] *tert*-Butyl 4-formylbenzoate was prepared from the commercially available 4-formylbenzoic acid employing *N*,*N*-dimethylformamide di-*tert*-butyl acetal[20] in refluxing PhMe. *N*-Phthalyl-L-valine and *N*-phthalyl-L-alanine were prepared according to the method of Bose[21] from L-valine and L-alanine, respectively. Toluene-*p*-sulfonyl-L-valine and toluene-*p*-sulfonyl-L-alanine were prepared according to the method of McChesney[14] from L-valine and L-alanine, respectively. Silver(I) oxide was freshly prepared before use according to the method of Schmitz.[22]

X-ray Crystallography. Table 2 provides a summary of the crystal data, data collection, and refinement parameters for compounds **9**, **10**, (2*S*)-**12c**, (2*R*)-**13a**. The structures were solved by direct methods and were refined by full matrix least-squares based on F^2. Due to a shortage of observed data, in (2*R*)-**13a** only the nitrogen, oxygen, and sulfur atoms were refined anisotropically. Also, in one of the two crystallographically independent molecules of this compound, disorder was found in one of the isopropyl groups—this was resolved into three overlapping one-third occupancy orientations. All of the non-hydrogen atoms in the other three structures were refined anisotropically. In each structure the hydrogen atoms were placed in calculated positions, assigned isotropic thermal parameters, $U(H) = 1.2U_{eq}(C)$[$U(H) = 1.5U_{eq}(C)$], and allowed to ride on their parent atoms. The absolute structures of all four compounds were determined by internal reference to the camphor moiety and independently by use of the Flack parameter (see Table 2). Computations were carried out using the SHELXTL PC program system.[23]

***N*,*N*-Diisopropyl-(1*R*)-10-thiocamphorsulfonamide (5).** Ketone **4** (1.00 g, 3.17 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-phosphetane 2,4-disulfide (Lawesson's reagent) (3.85 g, 9.52 mmol) were mixed in PhMe (80 mL) and heated at reflux for 12 h. The mixture was allowed to cool to room temperature, filtered through a plug of silica, and concentrated in vacuo. Chromatography (1:3 EtOAc:hexane; R_f 0.27) followed by recrystallization (hexane) gave thione **5** (0.86 g, 82%) as orange crystals, mp 92−93 °C; $[\alpha]_D^{23}$ +194.0° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 1332, 1185 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 3.92 (d, J = 14.5 Hz, 1H), 3.83 (m, 2H), 2.92 (d, J = 14.5 Hz, 1H,), 2.84−2.69 (m, 2H), 2.49 (d, J = 20.8 Hz, 1H), 2.17−2.09 (m, 2H), 1.63−1.40 (m, 2H), 1.36 (d, J = 6.8 Hz, 6H), 1.35 (d, J = 6.8 Hz, 6H), 1.26 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 266.0, 69.9, 55.0, 54.1, 49.8, 48.4, 45.1, 29.7, 27.1, 22.6, 22.1, 20.6, 19.8; *m*/*z* (CI^+; NH_3) 349 (M + $NH_4^{+\bullet}$), 332 (M + $H^{+\bullet}$), 102. Anal. Calcd for $C_{16}H_{29}NO_2S_2$: C, 57.98; H, 8.83; N, 4.23. Found: C, 57.97; H, 8.60; N, 4.19.

(1*S*)-10-(Diisopropylsulfamoyl)thioisoborneol (6). To a stirred solution of thione **5** (0.95 g, 2.87 mmol) in 2-propanol (19 mL) at 0 °C was added $NaBH_4$ (0.46 g, 12.2 mmol). After 10 min, the mixture was allowed to warm to room temperature, stirred for 3 h, poured into crushed ice (75 g), extracted with Et_2O (3 × 30 mL), dried ($MgSO_4$), and concentrated. Chromatography (1:9 EtOAc:hexane; R_f 0.31) followed by recrystallization (hexane) gave thiol **6** (0.87 g, 91%) as colorless crystals, mp 97.5−98 °C; $[\alpha]^{25}_D$−36.6° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2570, 1328 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 3.79 (m, 2H), 3.71 (d, J = 13.3 Hz, 1H), 3.45−3.40 (m, 1H), 2.71 (d, J = 13.4 Hz, 1H), 2.61 (d, J = 7.4 Hz, 1H), 2.11−1.95 (m, 2H), 1.79−1.54 (m, 4H), 1.33 (d, J = 6.8 Hz, 6H), 1.32 (d, J = 6.8 Hz, 6H), 1.30−1.20 (m, 1H), 0.95 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 54.6, 49.9, 49.7, 48.3, 45.3, 44.2, 40.2, 33.4, 27.3, 23.0, 22.0, 21.0, 20.1; *m*/*z* (CI^+, NH_3) 351 (M + $NH_4^{+\bullet}$), 334 (M + $H^{+\bullet}$). Anal. Calcd for $C_{16}H_{31}NO_2S_2$: C, 57.62; H, 9.37; N, 4.20. Found: C, 57.74; H, 9.21; N, 4.14.

[(1*S*)-10-(Diisopropylsulfamoyl)isobornylthio]nitromethane (8). To a solution of thiol **6** (1.53 g, 4.59 mmol) in CH_2Cl_2 (50 mL) maintained at −40 °C was added sulfuryl chloride (0.38 mL, 4.82 mmol). The solution was stirred for 4 h and then allowed to warm to room temperature. Concentration in vacuo gave the crude sulfenyl chloride **7** as a yellow oil (1.70 g). The ^{1}H NMR spectrum showed that **7** contained none of the starting material using the methylene proton at 2.71 ppm as a probe: ^{1}H NMR (300 MHz; $CDCl_3$) δ 3.92−3.79 (m, 3H), 3.54 (d, J = 13.8 Hz, 1H), 2.87 (d, J = 13.8 Hz, 1H), 2.40−2.00 (m, 3H), 1.89−1.72 (m, 3H), 1.37 (d, J = 6.8 Hz, 6H), 1.35 (d, J = 6.8 Hz, 6H), 1.31−1.22 (m, 1H), 0.92 (s, 3H), 0.82 (s, 3H). To a stirred solution of nitromethane (0.15 mL, 2.80 mmol)

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Table 2. Crystal Data, Data Collection and Refinement Parameters[a]

data	**9**	**10**	(2*S*)-**12c**	(2*R*)-**13a**
formula	$C_{19}H_{34}N_2O_4S_2$	$C_{21}H_{38}N_2O_4S_2$	$C_{20}H_{37}NO_4S_2$	$C_{29}H_{42}N_2O_5S_2$
formula weight	418.6	446.7	419.6	562.8
color, habit	yellow platy	clear prisms	clear platy needles	clear prisms
crystal size/mm	0.47 × 0.37 × 0.10	0.63 × 0.38 × 0.38	0.97 × 0.97 × 0.02	0.20 × 0.17 × 0.13
crystal system	monoclinic	orthorhombic	monoclinic	orthorhombic
space group	$P2_1$ (no. 4)	$P2_12_12_1$ (no. 19)	$P2_1$ (no. 4)	$P2_12_12_1$ (no. 19)
cell dimensions				
a/Å	9.769(1)	11.651(2)	11.077(5)	11.310(5)
b/Å	11.762(1)	11.669(1)	12.303(1)	12.460(2)
c/Å	10.925(1)	18.226(1)	17.518(2)	43.398(7)
β/deg	112.35(1)	−	99.95(2)	−
V/Å^3	1161.0(2)	2478.0(4)	2351(1)	6116(3)
Z	2	4	4[b]	8[b]
D_c/g cm^{-3}	1.197	1.197	1.185	1.222
F(000)	452	968	912	2416
radiation used	Cu−Kα[c]	Cu−Kα	Cu−Kα	Cu−Kα
μ/mm^{-1}	2.28	2.17	2.24	1.89
θ range/deg	4.4−63.0	4.5−63.5	2.6−63.0	2.0−50.0
no. of unique reflections				
measured	1979	2312	3994	3435
observed, $\|F_o\|$ $4\sigma(\|F_o\|)$	1811	2039	3431	2090
no. of variables	245	263	488	400
R_1[d]	0.053	0.060	0.072	0.095
wR_2[e]	0.138	0.160	0.192	0.231
weighting factors *a*, *b*[f]	0.088, 0.215	0.096, 0.886	0.153, 0.353	0.140, 14.716
Flack parameter	−0.03(5)	0.08(5)	0.03(9)	−0.12(9)
largest diff. peak, hole/eÅ^{-3}	0.29, −0.34	0.37, −0.27	0.44, −0.37	0.39, −0.40

[a] Details in common: graphite monochromated radiation, ω-scans, Siemens P4 diffractometer, 293 K, refinement based on F^2. [b] There are two crystallographically independent molecules in the asymmetric unit. [c] Rotating anode source. [d] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [e] $wR_2 = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$. [f] $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$.

in THF (10 mL) at −78 °C was added a solution of *n*-butyllithium in hexane (1.91 mL, 1.6 M, 3.06 mmol). After stirring for 1 h, the white suspension was added via cannula into a stirred solution of crude **7** (0.93 g, 2.55 mmol) in THF (10 mL) at −78 °C. After stirring for a further 1 h, the mixture was allowed to warm to room temperature. Water (5 mL) was added and the mixture concentrated in vacuo to remove all the solvents. The residue was dissolved in CH_2Cl_2 (40 mL), washed with water (40 mL) and brine (40 mL), dried ($MgSO_4$), and concentrated in vacuo to give a colorless oil. Chromatography (1:9 EtOAc:hexane; R_f 0.28) afforded **8** (0.49 g, 50%) as colorless crystals, mp 104−105 °C; $[\alpha]^{25}_D$ −58.3° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 1555, 1326 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 5.72 (d, *J* = 13.8 Hz, 1H), 5.20 (d, *J* = 13.8 Hz, 1H), 3.74 (m, 2H), 3.59 (d, *J* = 13.5 Hz, 1H), 3.40 (dd, *J* = 9.3, 5.4 Hz, 1H), 2.76 (d, *J* = 13.5 Hz, 1H), 2.27−2.10 (m, 3H), 1.81−1.64 (m, 3H), 1.34 (d, *J* = 6.8 Hz, 6H), 1.33 (d, *J* = 6.8 Hz, 6H), 1.31−1.25 (m, 1H), 0.88 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 80.4, 56.2, 54.6, 51.5, 49.3, 48.3, 45.4, 41.8, 33.5, 27.3, 22.9, 22.0, 20.5, 20.0; *m*/*z* (CI^+, NH_3) 410 (M + $NH_4^{+\bullet}$), 393 (M + $H^{+\bullet}$). Anal. Calcd for $C_{17}H_{32}N_2O_4S_2$: C, 52.01; H, 8.22; N, 7.14. Found: C, 52.31; H, 8.41; N, 7.08.

(*Z*)-1-[(1′*S*)-10′-(Diisopropylsulfamoyl)isobornylthio]-1-nitropropene (9). Nitroalkane **8** (0.41 g, 1.01 mmol), piperidinium acetate (14.7 mg, 0.10 mmol), and crushed 4 Å molecular sieves (0.5 g) in CH_2Cl_2 (10 mL) were cooled to 0 °C. Acetaldehyde (0.33 mL, 5.80 mmol) was added dropwise with stirring. After 30 min the mixture was allowed to warm to room temperature and was filtered through a plug of Celite, eluting with CH_2Cl_2 (20 mL). The filtrate was washed with aqueous 1 M HCl (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography (1:10 EtOAc: hexane; R_f 0.27) afforded nitroalkene **9** (0.28 g, 62%) as pale green crystals, mp 110−111 °C; $[\alpha]^{25}_D$ −28.4° (*c* 0.58, $CHCl_3$); IR ($CHCl_3$) 1528, 1331 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.62 (q, *J* = 7.3 Hz, 1H), 3.82 (m, 2H), 3.50 (d, *J* = 13.8 Hz, 1H), 3.46−3.38 (m, 1H), 2.78 (d, *J* = 13.8 Hz, 1H), 2.15 (d, *J* 7.3 Hz, 3H), 2.01−1.90 (m, 2H), 1.82−1.61 (m, 4H), 1.34 (d, *J* = 6.7 Hz, 6H), 1.33 (d, *J* = 6.8 Hz, 6H), 1.24 (m, 1H) 1.06 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 150.9, 141.1, 56.0, 54.2, 51.3, 49.5, 48.2, 45.4, 40.5, 33.8, 27.2, 23.1, 21.8, 20.7, 20.5, 16.2; *m*/*z* (CI^+, NH_3) 436 (M + $NH_4^{+\bullet}$), 419 (M + $H^{+\bullet}$); Anal. Calcd for $C_{19}H_{34}N_2O_4S_2$: C, 54.52; H, 8.19; N, 6.69. Found: C, 54.58; H, 7.98; N, 6.58.

(*Z*)-1-[(1′*S*)-10′-(Diisopropylsulfamoyl)isobornylthio]-1-nitro-3-methyl-1-butene (10). A solution of nitroalkane **8** (0.48 g, 1.22 mmol), isobutyraldehyde (0.22 mL, 2.44 mmol), and piperidinium acetate (18.0 mg, 0.12 mmol) in CH_2Cl_2 (40 mL) was heated at reflux with azeotropic removal of water using a Soxhlet apparatus charged with 4 Å molecular sieves for 5 h. The mixture was allowed to cool to room temperature, washed with aqueous 1 M HCl (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography on silica gel (1:10 ethyl acetate:hexane; R_f 0.29) gave nitroalkene **10** (0.43 g, 79%) as green crystals, mp 149−150 °C; $[\alpha]^{25}_D$ 36.2° (*c* 0.62, $CHCl_3$); IR ($CHCl_3$) 1529, 1325 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.32 (d, *J* = 10.5 Hz, 1H), 3.88−3.78 (m, 2H), 3.47 (d, *J* = 13.9 Hz, 1H), 3.45−3.41 (m, 1H), 3.12−3.06 (m, 1H), 2.82 (d, *J* = 13.9 Hz, 1H), 2.23−2.15 (m, 2H), 1.93−1.64 (m, 4H), 1.36 (d, *J* = 6.8 Hz, 6H), 1.35 (d, *J* = 6.8 Hz, 6H), 1.24−1.18 (m, 1H), 1.15 (d, *J* = 6.5 Hz, 3H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.07 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 151.7, 148.0, 56.2, 54.4, 51.4, 49.5, 48.2, 45.5, 40.2, 34.0, 30.1, 27.2, 23.1, 21.7, 20.7, 20.5; *m*/*z* (CI^+, NH_3) 464 (M + $NH_4^{+\bullet}$), 447 (M + $H^{+\bullet}$). Anal. Calcd for $C_{21}H_{38}N_2O_4S_2$: C, 56.47; H, 8.58; N, 6.27. Found: C, 56.23; H, 8.36; N, 6.21.

(*Z*)-2-[4″-(*tert*-Butyloxycarbonyl)phenyl]-1-[(1′*S*)-10′-(diisopropylsulfamoyl) isobornylthio]-1-nitroethene (11). A solution of nitroalkane **8** (50.0 mg, 0.13 mmol), *tert*-butyl 4-formylbenzoate (52.1 mg, 0.25 mmol), and piperidinium acetate (1.8 mg, 0.02 mmol) in CH_2Cl_2 (15 mL) was heated at reflux with azeotropic removal of water using a Soxhlet apparatus charged with 4 Å molecular sieves for 12 h. The mixture was allowed to cool to room temperature, washed with aqueous 1 M HCl (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography (1:10 EtOAc: hexane; R_f 0.26) gave nitroalkene **11** (52.4 mg, 71%) as yellow crystals, mp 131−132 °C; $[\alpha]^{25}_D$ −39.8° (*c* 0.62, $CHCl_3$); IR ($CHCl_3$) 1713, 1532, 1329 cm^{-1}; 1H NMR (300 MHz; $CDCl_3$) δ 8.22 (s, 1H,), 8.06 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.3 Hz,

2H), 3.54−3.41 (m, 4H), 2.68 (d, J = 13.7 Hz, 1H), 2.27−2.02 (m, 2H), 1.94−1.51 (m, 4H), 1.63 (s, 9H), 1.22 (d, J = 7.5 Hz, 6H), 1.19 (d, J = 7.5 Hz, 6H), 1.20 (m, 1H) 0.99 (s, 3H), 0.87 (s, 3H); m/z (CI^+, NH_3) 598 ($M + NH_4^{+\bullet}$), 581 ($M + H^{+\bullet}$). Anal. Calcd for $C_{29}H_{44}N_2O_6S_2$: C, 59.97; H, 7.64; N, 4.82. Found: C, 60.12; H, 7.38; N, 4.76.

General Procedure for the Tandem Conjugate Addition−Ozonolysis of Nucleophiles to Nitroalkenes 9−11. To a stirred solution of nitroalkene **9**, **10**, or **11** (30.0 mg) in DMF or 1:1 CH_2Cl_2:DMF (0.5 mL) at temperature T (Table 1) was added the representative nucleophile. Potassium phthalimide (18.5 mg, 0.10 mmol) and potassium trimethylsilanolate (13 mg, 0.10 mmol) were added as solids all in one portion. Potassium toluene-4-sulfonamide was generated from toluene-4-sulfonamide (13.5 mg, 0.07 mmol) in 1:1 CH_2Cl_2:DMF (0.4 mL) and a solution of potassium *tert*-butoxide in THF (86 μL, 1.0 M, 0.09 mmol) at 0 °C. NaOMe was added as a solution in MeOH (25 μL, 5M, 0.12 mmol) with DMF as cosolvent (0.2 mL). The homogeneous solution was stirred at temperature T for 6 h or until TLC demonstrated complete consumption of nitroalkene, diluted with CH_2Cl_2 (2.5 mL) and cooled to −78 °C. In the cases where NaOMe was the nucleophile the mixture was instead diluted with MeOH (2.5 mL) and similarly cooled to −78 °C. Ozone was bubbled through the mixture until the characteristic faint blue color persisted (ca. 5 min). After quenching with water (2 mL), the mixture was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with water (4 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification was effected by flash column chromatography (EtOAc:hexane). When potassium trimethylsilanolate had been used as the nucleophile the residue after evaporation was instead taken up in 10% citric acid in MeOH (1 mL) and stirred for 1 h before being poured into water (5 mL), extracted with EtOAc (3 × 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure followed by flash column chromatography (EtOAc:hexane).

General Procedure for the 1-(3-Dimethylamino)propyl)-3-ethylcarbodiimide Hydrochloride Mediated Coupling of Thiol 6 with Enantiomerically Pure α-Substituted Carboxylic Acid Derivatives. 1-(3-(Dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI) (49 mg, 0.26 mmol) was added to a stirred solution of carboxylic acid (0.21 mmol), DMAP (1.8 mg, 0.02 mmol), and thiol **6** (71 mg, 0.21 mmol) in DMF (0.3 mL) (for **12a**, **12b**, **13a**, and **13b**) or CH_2Cl_2 (0.3 mL) (for **12c**) at 0 °C. The mixture was allowed to warm and stirred at room temperature for 5 h. The solution was diluted with CH_2Cl_2 (10 mL), washed with water (5 × 15 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (EtOAc:hexane).

***S*-[(1′*S*,2′*R*)-10′-(Diisopropylsulfamoyl)isobornyl] (2*R*,*S*)-Phthalimidopropanethioate (12a).** Tandem conjugate addition−ozonolysis of potassium phthalimide to nitroalkene **9** and purification by chromatography on silica gel (1:6 EtOAc:hexane; R_f 0.27) afforded thioester **12a** (25.0 mg, 65%) as a 1:1 mixture of the 2*R* and 2*S* epimers as a colorless oil: IR ($CHCl_3$) 1778, 1720, 1695, 1331 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 7.91−7.84 (m, 4H), 7.81−7.74 (m, 4H), 5.03−4.95 (m, 2H), 4.15−4.06 (m, 2H), 3.80−3.69 (m, 4H), 3.11 (br d, J = 13.7 Hz, 2H), 2.76 (d, J = 13.8 Hz, 1H), 2.70 (d, J = 13.7 Hz, 1H), 2.26−2.06 (m, 4H), 1.81−1.51 (m, 14H), 1.37−1.28 (m, 26H), 0.92 (s, 3H), 0.86 (s, 6H), 0.78 (s, 3H); m/z (CI^+, NH_3) 552 ($M + NH_4^{+\bullet}$), 535 ($M + H^{+\bullet}$), HRMS (CI) Calcd for $C_{27}H_{42}N_3O_5S_2$: 552.2570 ($M + NH_4^{+\bullet}$). Found: 552.2566. Anal. Calcd for $C_{27}H_{38}N_2O_5S_2$: C, 60.65; H, 7.16; N, 5.24. Found: C, 60.79; H, 7.33; N, 5.26. The mixture of epimers was identical to that obtained from the EDCI-mediated coupling of thiol **6** with *N*-phthalyl-L-alanine where presumably a fast epimerization occurred.

***S*-[(1′*S*,2′*R*)-10′-(Diisopropylsulfamoyl)isobornyl] (2*R*,*S*)-(*p*-Toluenesulfamoyl)propanethioate (12b).** Tandem conjugate addition−ozonolysis of potassium toluene-4-sulfonamide to nitroalkene **9** and purification by chromatography (2:7 EtOAc:hexane; R_f 0.25) afforded thioester **12b** (28.8 mg, 72%) as a 2.0:1 mixture of the 2*R* and 2*S* epimers as a colorless oil: IR ($CHCl_3$) 3266, 1687, 1331 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 7.72 (m, 2H), 7.29 (m, 2H), 5.26 (d, J = 9.1 Hz, 0.67H), 5.12 (d, J = 8.0 Hz, 0.33H), 4.20−4.08 (m, 1H), 3.91−3.87 (m, 1H), 3.78−3.69 (m, 2H), 3.11 (m, 1H), 2.69 (m, 1H), 2.42 (s, 3H), 2.25−2.02 (m, 2H), 1.99−1.69 (m, 4H), 1.33−1.29 (m, 16H) 0.90 (s, 1H), 0.89 (s, 2H), 0.87 (s, 2H), 0.84 (s, 1H); m/z (CI^+, NH_3) 576 ($M + NH_4^+$); HRMS (CI) Calcd for $C_{26}H_{46}N_3O_5S_3$: 576.2600. Found: 576.2603 ($M + NH_4^+$). The minor 2*S* epimer prepared as a colorless oil from the EDCI mediated coupling of thiol **6** with toluene-*p*-sulfonyl-L-alanine followed by chromatography (2:7 EtOAc:hexane; R_f 0.25) (33 mg, 28%) displayed the following spectral characteristics: $[\alpha]^{25}_D$ −22.0° (*c* 0.83, $CHCl_3$); ^1H NMR (300 MHz; $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 5.12 (d, J = 8.1 Hz, 1H), 4.19−4.11 (m, 1H), 3.97−3.92 (m, 1H), 3.78−3.67 (m, 2H), 3.13 (d, J = 13.8 Hz, 1H), 2.75 (d, J = 13.7 Hz, 1H), 2.42 (s, 3H), 2.20−2.01 (m, 2H), 1.82−1.64 (m, 4H), 1.35−1.29 (m, 16H), 0.90 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 197.3, 177.7, 158.8, 129.8, 127.1, 58.5, 54.9, 50.6, 49.7, 48.2, 48.1, 48.0, 45.5, 40.8, 33.9, 27.3, 22.8, 22.1, 21.6, 20.5, 20.2; m/z (CI^+, NH_3) 576 ($M + NH_4^{+\bullet}$), 559 ($M + H^{+\bullet}$); HRMS (CI) Calcd for $C_{26}H_{43}N_2O_5S_3$: 559.2334. Found: 559.2335 ($M + H^{+\bullet}$).

***S*-[(1′*S*,2′*R*)-10′-(Diisopropylsulfamoyl)isobornyl] (2*R*,*S*)-Methoxypropanethioate (12c).** Tandem conjugate addition−ozonolysis of NaOMe to nitroalkene **9** and purification by chromatography (1:10 EtOAc:hexane, R_f 0.20) afforded thioester **12c** (12.7 mg, 32%) as a 3.1:1 mixture of the 2*R* and 2*S* epimers as a colorless oil: IR ($CHCl_3$) 1688, 1332 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 5.01 (m, 1H), 4.04 (dd, J = 9.2, 4.9 Hz, 0.33H) 3.88−3.61 (m, 4H), 3.43 (s, 1H), 3.41 (s, 3H), 3.30−3.20 (m, 1.33H), 2.81−2.62 (m, 1.33H), 2.10−1.95 (m, 2.67H), 1.93−1.80 (m, 5.33H), 1.39 (d, J = 6.5 Hz, 3H), 1.36−1.18 (m, 18.33H), 1.00 (s, 3H), 0.95 (s, 1H), 0.92 (s, 1H), 0.90 (s, 3H); m/z (CI^+, NH_3) 437 ($M + NH_4^{+\bullet}$), 420 ($M + H^{+\bullet}$); HRMS (CI) Calcd for $C_{20}H_{38}NO_4S_2$:420.2242. Found 420.2235 ($M + H^{+\bullet}$). The minor 2*S* epimer prepared as colorless crystals from the EDCI-mediated coupling of thiol **6** with (*S*)-carboxylic acid **17** followed by chromatography (1:10 EtOAc:hexane; R_f 0.20) (56.3 mg, 64%) displayed the following spectral characteristics: mp 92.5−93 °C (from hexane); $[\alpha]^{25}_D$ −26.2° (*c* 0.51, $CHCl_3$); ^1H NMR (300 MHz; $CDCl_3$) δ 4.04 (dd, J = 9.2, 4.9 Hz, 1H), 3.87 (q, J = 6.7 Hz, 1H), 3.78−3.68 (m, 2H), 3.43 (s, 3H), 3.22 (d, J = 13.7 Hz, 1H), 2.69 (d, J = 13.7 Hz, 1H), 2.15−2.07 (m, 2H), 1.88−1.70 (m, 4H), 1.37 (d, J = 6.7 Hz, 3H), 1.37−1.28 (m, 1H), 1.30 (d, J = 6.8 Hz, 12H) 0.94 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 200.8, 83.5, 58.3, 54.7, 50.5, 49.5, 48.1, 46.6, 45.7, 41.1, 34.0, 27.3, 22.9, 21.9, 20.6, 20.3, 19.0; m/z (CI^+, NH_3) 437 ($M + NH_4^{+\bullet}$), 420 ($M + H^{+\bullet}$); HRMS (CI) Calcd for $C_{20}H_{38}NO_4S_2$: 420.2242. Found: 420.2236 ($M + H^+$). Anal. Calcd for $C_{20}H_{37}NO_4S_2$: C, 57.24; H, 8.89; N, 3.34. Found: C, 57.21; H, 8.65; N, 3.30.

***S*-[(1′*S*,2′*R*)-10′-(Diisopropylsulfamoyl)isobornyl] (2*R*)-3-Methyl-2-phthalimidobutanethioate (13a).** Tandem conjugate addition−ozonolysis of potassium phthalimide to nitroalkene **10** and purification by chromatography (1:6 EtOAc:hexane; R_f 0.27) afforded thioester **13a** (23.1 mg, 61%) as a 5.8:1 mixture of the 2*R* and 2*S* epimers. The major 2*R* epimer was isolated after two recrystallizations (from hexane) as colorless crystals: mp 115−116 °C; $[\alpha]^{25}_D$ −41.4° (*c* 0.82, $CHCl_3$); IR ($CHCl_3$) 1722, 1331 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 7.93−7.88 (m, 2H), 7.82−7.75 (m, 2H), 4.53 (d, J = 9.5 Hz, 1H), 4.13−4.07 (m, 1H), 3.80−3.70 (m, 2H), 3.14 (d, J = 13.7 Hz, 1H), 2.95−2.86 (m, 1H), 2.69 (d, J = 13.7 Hz, 1H), 2.17−2.09 (m, 2H), 1.87−1.71 (m, 4H), 1.35 (d, J = 6.8 Hz, 6H), 1.33−1.22 (m, 1H), 1.31 (d, J = 6.8 Hz, 6H), 1.17 (d, J = 6.5 Hz, 3H), 0.86 (s, 3H), 0.83 (d, J = 6.8 Hz, 3H), 0.76 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 192.9, 167.5, 134.3, 132.0, 123.7, 65.0, 54.6, 50.7, 49.4, 48.3, 48.2, 45.5, 40.9, 33.8, 27.7, 27.3, 22.9, 21.8, 21.1, 20.6, 20.2, 19.3; m/z (CI^+, NH_3) 580 ($M + NH_4^{+\bullet}$); HRMS (CI^+, NH_3) Calcd for $C_{29}H_{46}N_3O_5S_2$: 580.2879. Found: 580.2876 ($M + NH_4+$). Anal. Calcd for $C_{29}H_{42}N_2O_5S_2$: C, 61.89 H, 7.52 N, 4.98. Found: C, 61.71; H, 7.75; N, 4.73. The minor 2*S* epimer prepared as a colorless oil from the EDCI-mediated coupling of thiol **6** with *N*-phthalyl-L-valine followed by chromatography (1:6 EtOAc:

hexane; R_f 0.22) (32.8 mg, 28%) displayed the following spectral characteristics: ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.90−7.84 (m, 2H), 8.00−7.73 (m, 2H), 4.59 (d, J = 9.7 Hz, 1H), 4.04 (dd, J = 8.9, 4.9 Hz, 1H), 3.72−3.62 (m, 2H), 3.06 (d, J = 13.8 Hz, 1H), 3.06−2.98 (m, 1H), 2.73 (d, J = 13.8 Hz, 1H), 2.31−2.08 (m, 2H), 1.89−1.72 (m, 4H), 1.35−1.20 (m, 13H), 1.14 (d, J = 6.6 Hz, 3H), 0.90−0.87 (m, 9H); m/z (CI^+, NH_3) 580 (M + NH_4+), 563 (M + H^+).

***S*-[(1′*S*,2′*R*)-10′-(Diisopropylsulfamoyl)isobornyl] (2*R*,*S*)-3-Methyl-2-(*p*-toluenesulfamoyl)butanethioate (13b).** Tandem conjugate addition−ozonolysis of potassium toluene-4-sulfonamide to nitroalkene **10** and purification by chromatography (2:7 EtOAc:hexane; R_f 0.27) afforded thioester **13b** (28.0 mg, 71%) as a 3.0:1 mixture of the 2*R* and 2*S* epimers as a colorless oil: IR ($CHCl_3$) 3275, 1681, 1331 cm^{-1}; 1H NMR (300 MHz; $CDCl_3$) δ 7.70 (d, J = 8.2 Hz, 2H), 7.29 (m, 2H), 5.29 (d, J = 10.0 Hz, 0.75H), 4.96 (d, J = 9.6 Hz, 0.25H), 4.04 (m, 0.25H), 3.85−3.79 (m, 1.75H), 3.74−3.67 (m, 2H), 3.01 (d, J = 13.7 Hz, 0.25H), 3.00 (d, J = 13.7 Hz, 0.75H), 2.75 (d, J = 13.7 Hz, 0.25H) 2.66 (d, J = 13.7 Hz, 0.75H), 2.41 (s, 0.75H), 2.40 (s, 2.25H), 2.12−1.99 (m, 2H), 1.85−1.47 (m, 5H), 1.28 (m, 13H), 1.04 (d, J = 6.8 Hz, 2.25H), 0.99 (d, J = 6.4 Hz, 0.75H) 0.90−0.80 (m, 9H); m/z (CI^+, NH_3) 604 (M + $NH_4^{+\bullet}$), 587 (M + $H^{+\bullet}$); HRMS (CI^+, NH_3) Calcd for $C_{28}H_{50}N_3O_5S_3$: 604.2910. Found: 604.2911 (M + $NH_4^{+\bullet}$). The minor 2*S* epimer prepared as a colorless oil from the EDCI-mediated coupling of thiol **6** with toluene-*p*-sulfonyl-L-valine followed by chromatography (2:9 EtOAc:hexane; R_f 0.27) (67.6 mg, 48%) displayed the following spectral characteristics: $[\alpha]^{25}_D$ −37.3° (*c* 0.99, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 5.08 (d, J = 9.6 Hz, 1H), 4.02 (dd, J = 9.6, 4.6 Hz, 1H), 3.87−3.81 (m, 1H), 3.75−3.65 (m, 2H), 3.02 (d, J = 13.8 Hz, 1H), 2.73 (d, J = 13.7 Hz, 1H), 2.41 (s, 3H), 2.21−1.98 (m, 3H), 1.80−1.72 (m, 3H), 1.61−1.49 (m, 1H), 1.31−1.21 (m, 1H), 1.30 (d, J = 6.8 Hz, 12H), 0.91 (d, J = 6.8 Hz, 3H), 0.88 (s, 3H), 0.83 (d, J = 6.8 Hz, 3H), 0.82 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 197.3, 143.6, 137.5, 129.8, 127.1, 68.0, 54.9, 50.2, 49.7, 48.6, 48.2, 45.5, 41.1, 33.9, 32.1, 27.2, 22.9, 22.0, 21.6, 20.6, 20.3, 19.4, 16.6.

***S*-[(1′*S*,2′*R*)-10′-(Diisopropylsulfamoyl)isobornyl] (2*R*,*S*)-2-[4-(*tert*-Butoxycarbonyl)phenyl]-2-hydroxyethanethioate (14a).** Tandem conjugate addition−ozonolysis of $KOSiMe_3$ to nitroalkene **11** and purification by chromatography (1:6 EtOAc:hexane; R_f 0.15) afforded thioester **14a** (21.7 mg, 74%) as a 2.3:1 mixture of the 2*R* and 2*S* epimers as a colorless oil: IR ($CHCl_3$) 3452, 1711, 1686, 1331 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.97 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 8.3 Hz, 1.4H), 7.46 (d, J = 8.2 Hz, 0.6H) 5.23 (s, 0.7H), 5.21 (s, 0.3H), 4.13−4.10 (m, 1H), 3.73−3.68 (m, 0.6H), 3.44−3.38 (m, 1.4H), 3.13 (d, J = 13.7 Hz, 0.3H), 2.90 (d, J = 13.6 Hz, 0.7H), 2.73 (d, J = 13.7 Hz, 0.3 H), 2.63 (d, J = 13.6 Hz, 0.7H), 2.17−2.04 (m, 2H), 1.85−1.73 (m, 4H), 1.58 (s, 6.3H), 1.57 (s, 2.7H), 1.33−1.25 (m, 4.6H), 1.14−1.11 (m, 12H), 0.87 (m, 5.1H), 0.80 (s, 0.9H); m/z (CI^+, NH_3) 585 (M + $NH_4^{+\bullet}$), 569 (M + $H^{+\bullet}$); HRMS (CI^+, NH_3) Calcd for $C_{29}H_{49}N_2O_6S_2$: 585.3032. Found: 585.3029 (M + NH_4+).

***(S)*-Ethyl 2-Methoxypropanoate (16).** To a solution of (*S*)-(−)-ethyl lactate (**15**) (0.50 g, 4.23 mmol) in MeCN (2.7 mL) was added MeI (2.17 mL, 33.8 mmol) followed by silver oxide (1.08 g, 4.68 mmol). The mixture was heated at reflux for 5 h with vigorous stirring. After being allowed to cool to room temperature, the reaction mixture was filtered through Celite, eluting with CH_2Cl_2 (20 mL). The resulting solution was washed with water (2 × 15 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Short path distillation of the crude product (pot temperature 50 °C, 20 mmHg) afforded the ester **16** (0.51 g, 92%) as a colorless oil: $[\alpha]^{25}_D$ −115.9° (*c* 1.05, $CHCl_3$) (lit.[24] −116.4°, neat); ^{1}H NMR (300 MHz; $CDCl_3$) δ 4.20 (q, J = 7.1 Hz, 2H), 3.85 (q, J = 6.8 Hz, 1H), 3.38 (s, 3H), 1.38 (d, J = 6.8 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 173.1, 76.4, 60.8, 57.6, 18.4, 14.2; m/z (CI^+, NH_3) 150 (M + $NH_4^{+\bullet}$), 133; HRMS (CI^+, NH_3) Calcd for $C_6H_{16}NO_3$: 150.1130. Found: 150.1128 (M + $NH_4^{+\bullet}$).

***(S)*-2-Methoxypropionic Acid (17).** Cooled aqueous 0.20 M LiOH (7.6 mL, 1.51 mmol) was added dropwise over 10 min to ester **16** (0.10 g, 0.76 mmol) in THF (7.6 mL) at 0 °C. After being stirred at room temperature for 3 h, the solution was concentrated in vacuo to one-half volume. The resulting aqueous mixture was acidified with aqueous 5% HCl and extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo to afford the carboxylic acid **17** (76.4 mg, 97%) as a colorless oil: $[\alpha]^{25}_D$ −70.9° (*c* 1.00, $CHCl_3$) (lit.[25] −70.4°, neat); ^{1}H NMR (300 MHz; $CDCl_3$) δ 10.5−9.2 (br s, 1H) 3.95 (q, J = 6.9 Hz, 1H), 3.47 (s, 3H), 1.48 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 178.1, 76.0, 57.8, 18.0; m/z (CI^+, NH_3) 122 (M + $NH_4^{+\bullet}$); HRMS (CI^+, NH_3) Calcd for $C_4H_{12}NO_3$: 122.0817. Found: 122.0819 (M + $NH_4^{+\bullet}$).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of (*S*)-**12b**, (*S*)-**13b**, and (2*R*,*S*)-**14a** (^{1}H NMR only) and X-ray crystallographic data for **9**, **10**, (2*S*)-**12c**, and (2*R*)-**13a** (36 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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