Synthesis of Sulfur-Containing Olefinic Peptide Mimetic Farnesyl Transferase Inhibitors Using the Nozaki−Hiyama−Kishi Reaction and Cuprate S_N2' Displacements

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Syntheses of the potent sulfur-containing tetrapeptide mimetic farnesyl transferase inhibitors B956 (**22**) and B957 (**23**) are described. The two double bonds in **22** and **23** were constructed by application of iterative NHK and cuprate S_N2' reactions. Normal *syn* NHK reaction and substrate-dependent *syn* and *anti*-S_N2' diastereoselectivities accompanied by exclusive *E*-olefin selectivity were observed for the first NHK iteration (**1** → **4**). In the second iteration, unexpected epimerization and a strong preference for *syn* diastereoselectivity was observed for the NHK reaction (**5b** → **7a** + **9a**) while an unusual *Z*-olefin was observed for the S_N2' reaction (**7b** → **11**). Deprotection conditions were optimized to ensure high purity and yield of the final aminothiol compounds.

Introduction

Farnesyl transferase (FT) covalently attaches the farnesyl group of farnesyl pyrophosphate (FPP) to a cysteine thiol of its protein substrate.[1,2] FT is one of three known isoprenyl-protein transfer enzymes; the remaining two, geranylgeranyl transferases I and II (GGT-I, GGT-II), transfer a geranylgeranyl group to their respective substrates.[3] FT and GGT-I share consensus recognition elements in their respective target proteins: the putative C-terminal CA_1A_2X box sequence. Interest in these enzymes has arisen out of the unique nature of the lipid modifications they mediate and the importance of their protein substrates in critical cellular processes such as growth regulation, signaling, and intracellular transport. One substrate in particular, the small G protein ras,[4] has generated an enormous amount of interest in FT. Inhibition of oncogenic ras function through inhibition of ras posttranslational farnesylation offers the potential for a novel, rational mechanistic approach to anticancer therapy. Many groups have reported on the successful in vitro and in vivo inhibition of ras farnesylation with CAAX-derived peptides[1,5] and peptidomimetics.[6] At least two agents have been reported to be under clinical study.[7]

Interest in targeting FT inhibition lead us to consider developing peptidomimetics based upon CAAX tetrapeptides. We and others have hypothesized that the nature of the two interior residues of the CAAX peptides, typically bulky hydrophobic residues, served to confer a bent or turn configuration to the inhibitors.[8,9] Isosteric replacement of the interior peptide bonds with olefins might serve to increase the hydrophobic nature of the

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inner portion of the molecule and further stabilize such bent conformations. In addition, it was shown that replacement of the proteolytically unstable N-terminal amide bonds in tetrapeptide inhibitors was necessary to demonstrate inhibition of FT function in whole cells.[10] Substitution of the amide bonds with olefins would represent an attractive means to achieve proteolytic stability.[11] While this approach is not novel, it has been underutilized within the context of sulfur-containing amino acids characteristic of the FT tetrapeptide inhibitors. The presence of sulfur sharply limits the extent to which oxidative conditions may be utilized to prepare these materials and presented a challenge for the development of inhibitors. Novel chemistry is required to prepare such materials within this constraint.

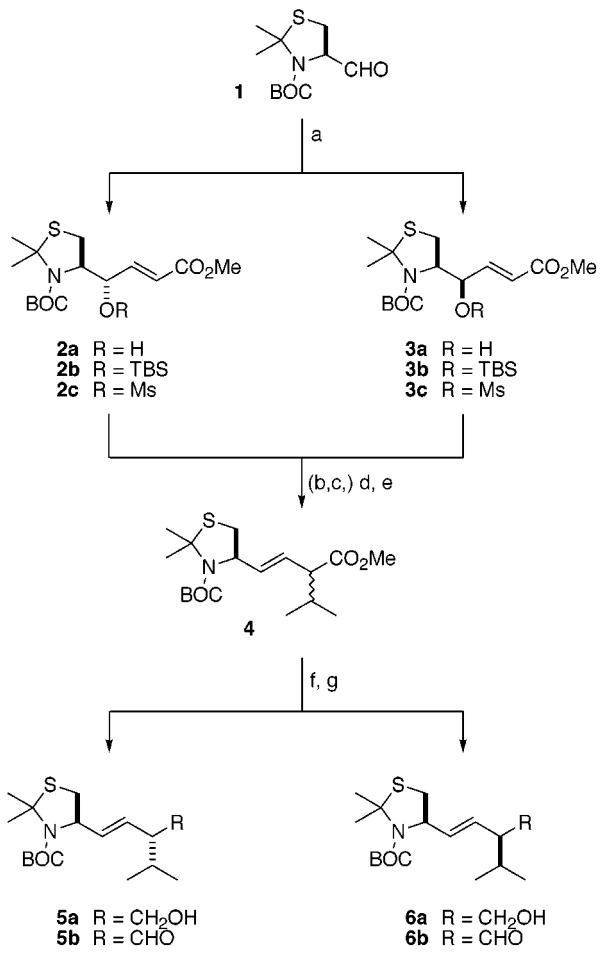
The configuration of the asymmetric A_2 α center in a previously reported series of monosubstituted straight chain alkyl carbon-linked tetrapeptide mimetics was demonstrated to be important in determining the FT/GGT-I specificity of the inhibitors.[12] It was intriguing to speculate that it might be possible to manipulate the enzymatic specificity further in the stereochemically defined environment of the proposed olefin-derived mimetics by adjusting the substitution and configuration at the asymmetric α center of A_2. Selectivity of FT over GGT-I may be critical with respect to the toxicity of the inhibitors and/or their ability to completely inhibit the processing of specific forms of ras, which in the presence of FT inhibitors may be alternatively processed through GGT-I.[13] Such manipulations might be accessible through a general, well-characterized synthetic route for the construction of olefinic peptide mimetics. With these objectives in mind, we set out to investigate syntheses of bis-olefin mimetics of the prototype FT tetrapeptide inhibitor, CVFM.

Results and Discussions

A general method for the construction of olefinic peptide isosteres is the S_N2' reaction of organometallic reagents RCu(CN)MgX·BF_3 with γ-(mesyloxy)-α,β-enoates as reported by Ibuka, Fujii, and Yamamoto.[14] The precursor alcoholic enoates are in turn derived from the treatment of amino acid aldehydes with vinyl Grignard reagents, followed by ozonolysis and reaction with (carbomethoxymethyl)triphenylphosphorane. Although this sequence is tolerant of many functional groups, the presence of sulfur in the proposed bis-olefinic CVFM mimetics such as B957 (**23**) necessitated using a modified approach.

The Nozaki−Hiyama−Kishi (NHK) reaction has been shown to be a very tolerant method for the construction of carbon−carbon bonds in the presence of reactive and oxidatively sensitive functionality.[15] Moreover, β-iodoacrylates react very well under these conditions to afford γ-hydroxyenoate products.[16] Reaction with aldehydes derived from amino acids would permit the convenient preparation of the Yamamoto S_N2' substrate precursors.

Scheme 1[a]



[a] (a) (2*Z*)-3-Iodoacrylate, $CrCl_2$, $Ni(COD)_2$, THF, rt, 65%; (b) TBSOTf, CH_2Cl_2, TEA, 64%; (c) TBAF, HOAc, THF, quant; (d) MsCl, TEA, CH_2Cl_2, 0 °C, 94%; (e) CuCN, *i*-PrMgCl, THF, BF_3OEt_2, 0 °C; **2c** or **3c**, −78 °C, ∼90%; (f) DIBAL, hexanes, PhMe, rt, 97%; (g) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C; **5a** or **5b**; TEA; 91−95%.

Thus, methyl (2*Z*)-3-iodoacrylate was reacted with aldehyde **1**[17] under modified NHK conditions to afford a ∼1:2.5 ratio of the desired adducts **2a** and **3a** in a combined yield of 55−65% (Scheme 1). Although modest, this product ratio is consistent with the nonchelating preference usually observed under these conditions. The configuration of **3a** was confirmed by an NOE experiment on a bicyclic derivative.[18] It was not possible to repro-

(10) See ref 6a above.
(11) See for example (a) Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4875. (b) Wipf, P.; Henninger, T. C. *Ibid.* **1997**, *62*, 1586 and references contained therein.
(12) See ref 6f above.
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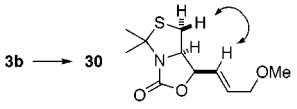
(18) Silylated alcohol **3b** was treated with (a) LAH, THF, 0 °C; (b) NaH, MeI, THF; (c) TBAF, HOAc, THF; (d) NaH, DMF to afford the following bicyclic compound **30** which exhibited an NOE between the indicated protons.

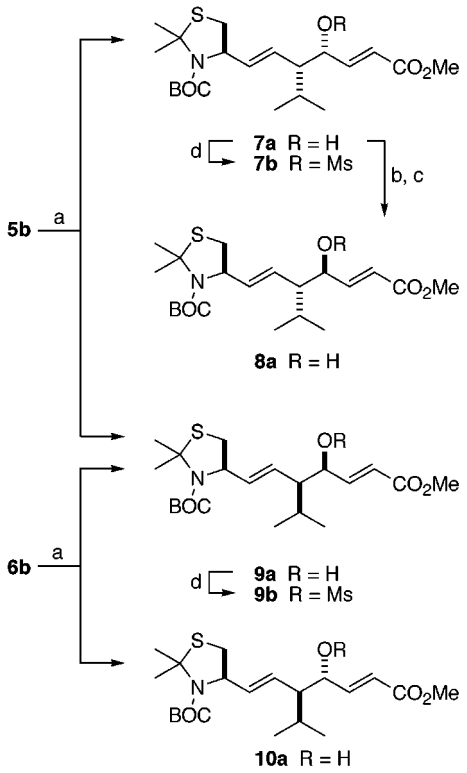


ducibly achieve chromatographic baseline separation of alcohols **2a** or **3a** with any degree of efficiency. Consequently, for the purpose of establishing the course of the succeeding S_N2' reaction, alcohols **2a** and **3a** were converted to their *tert*-butyldimethylsilyl ethers **2b** and **3b**, the diastereomers separated, and then individually desilylated. Mesylation of alcohol **2a** or **3a** followed by treatment with the reagent formed from the addition of BF_3OEt_2 to a mixture of *i*-PrMgBr and CuCN afforded an excellent yield of diastereomeric S_N2' products **4** in approximate ratios of 4.4:1 and 1:2.4 *syn*:*anti* directions of reagent attack, respectively. In both cases, proceeding from either **2c** or **3c**, the configuration of the newly transposed stereogenic center was predominantly (*R*). This configuration was confirmed by later X-ray analyses of two compounds derived from **4** (**7a** and **12**, see below). In routine practice it was convenient to forego the silylation, carry forward a mixture of **2a** and **3a**, and to separate the diastereomers after DIBAL reduction to the corresponding allylic alcohols **5a** and **5b**. The observed stereoselectivity is analogous to the S_N2' displacement reported for the related serine-derived series and represents in the case of mesylate **2c**, a substrate-dependent shift of the normal direction of reagent attack from *anti* to *syn*.[14c] This phenomenon is seen with substrates possessing bulky substitution around the reacting olefin, in this case represented by the N-BOC dimethylthiazolidine ring which exerts its steric bulk in a manner similar to its oxygen counterpart. DIBAL reduction of **4** followed by oxidation afforded access to either the predominant (2*R*)-diastereomer **5b** or its minor (2*S*)-isomer **6b**. Unfortunately it was not possible to directly hydrolyze methyl ester **4** without decomposition, presumably due to the steric hindrance of the α-isopropyl substituent.

To establish the second olefin, aldehydes **5b** and **6b** were separately and iteratively treated with (2*Z*)-3-iodoacrylate under the same modified NHK reaction conditions (Scheme 2). Interestingly, although the diastereomeric product ratios appeared similar, ~6:1 for reaction with **5b** and ~4:1 for reaction with **6b**, the product composition indicated a differing course of reaction for these two diastereomers. Aldehyde **6b** reacts to afford the expected major *syn* alcohol **9a** and its minor *anti* diastereomer **10a**. However, NHK reaction of (2*Z*)-3-iodoacrylate with aldehyde **5b** predominantly afforded the expected *syn* isomer **7a** and the epimerized *syn* diastereomer **9a**. None of the expected *anti* diastereomer **8a** could be detected by HPLC analysis of the crude reaction product from **5b** and no similar epimerized product was detected in reactions using **6b**. To confirm these stereochemical assignments, an authentic sample of diastereomer **8a** was prepared by oxidation of **7a** followed by stereorandom reduction of the resulting enone. Final confirmation of structure for **7a** was obtained by X-ray crystallographic analysis (Figure 1). It is remarkable that the dimethylthiazolidine ring exerts such a substantial influence across the *E* olefin on the relative configuration of the isopropyl-bearing stereocenter during the course of the NHK reaction.

Syn adduct **7a** was mesylated to provide **7b** which was subjected to S_N2' displacement with the reagent derived from BnMgCl, CuCN, and BF_3OEt_2 (Scheme 3). As expected, two products were obtained from this reaction in a ratio of ~2:1. Remarkably, minor isomer **14** was the expected *E*-olefinic product arising from the *anti* S_N2' reaction while major isomer **11** possessed a *Z*-olefin, a somewhat unusual S_N2' reaction product. Confirmation of the configuration of the newly generated stereogenic benzyl center was performed both by a short sequence of chemical degradation and subsequent correlation with known materials,[19] and by X-ray crystallographic analy-

Scheme 2[a]



[a] (a) (2*Z*)-3-Iodoacrylate, $CrCl_2$, $Ni(COD)_2$, THF, rt, 68−79%; (b) Dess−Martin reagent, 4 Å mol sieves, *t*-BuOH; CH_2Cl_2; (c) $NaBH_4$, MeOH, 0 °C; (d) MsCl, TEA, CH_2Cl_2, 77−86%.

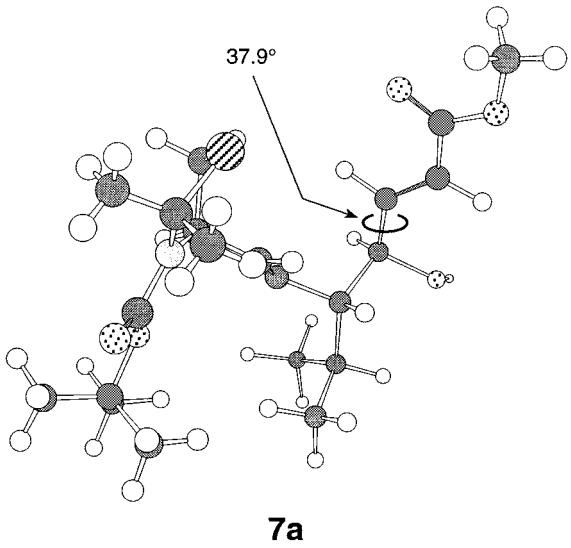
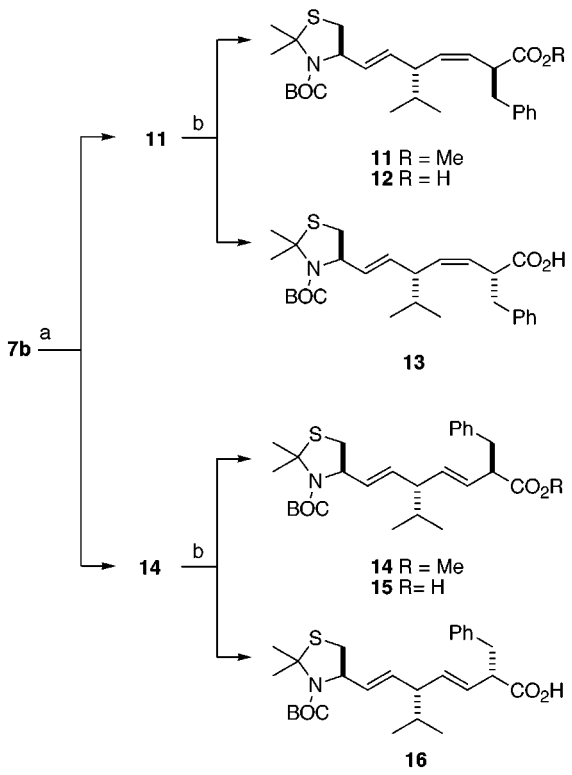


Figure 1.

(19) Successive reaction of **11** with (a) LAH; b) NaH, BnBr; (c) O_3, MeOH; (d) $NaBH_4$ afforded isolation of (*S*)-2-[(phenylmethoxy)methyl]-3-benzenepropanol, $[\alpha]_D = -27°$ (*c* 0.25, $CHCl_3$). Similar treatment of **15** afforded isolation of the (*R*) enantiomer, $[\alpha]_D = +24°$ (*c* 0.95, $CHCl_3$). (*R*)-2-[(Phenylmethoxy)methyl]-3-benzenepropanol has a reported optical rotation of +33.1° (*c* 1.32, $CHCl_3$) by Aebi, J. D.; Sutter, M. A.; Wasmuth, D.; Seebach, D. *Liebigs Ann. Chem.* **1983**, *12*, 2114.

Scheme 3[a]



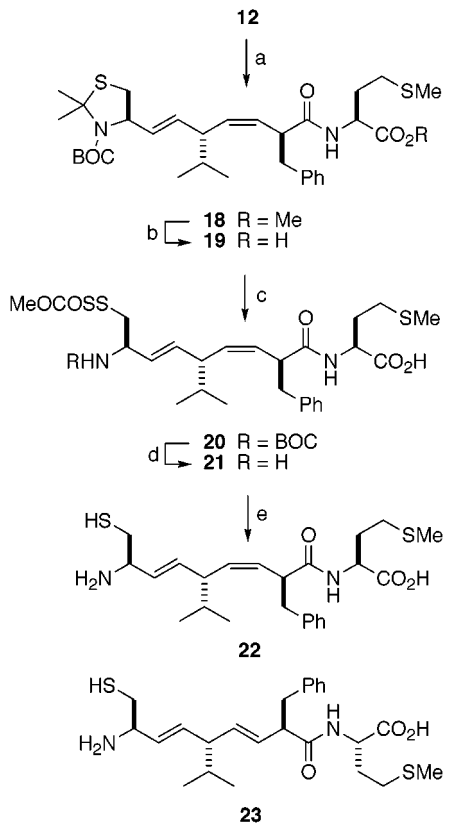
[a] (a) CuCN, BnMgCl, THF, −20 °C to rt; **7b**, −78 °C, 89%; (b) LiOH, H_2O, dioxane, ∼85%.

sis of **12**. In contrast to the first S_N2' reaction, *syn* reagent attack was not observed. Hydrolysis of methyl ester **11** afforded both the expected product **12** and small quantities of a material assigned the structure of the epimerized product **13** in a ratio of 27:1. However, identical hydrolysis conditions applied to **14** yielded a 2:1 ratio of the corresponding mixture of expected **15** and the proposed epimerized **16**. Interestingly, when the mesylate **9b** was subjected to the S_N2' displacement with the same benzyl copper mixture, an even higher *Z*-olefin selectivity (≥6.8:1) was observed, affording a compound assigned the structure of **17** by presumed exclusive *anti* attack of the reagent (Scheme 5).

The synthesis of B956 (**22**) was completed in a straightforward manner as depicted in Scheme 4. Although the individual transformations for deprotection of the cysteine-like functionality are not novel, the precise sequence was critical to the preparation of final products in high yields and in >95% purity. B957 (**23**) was prepared uneventfully from **15** in an analogous manner to B956 (**15** → **24** → **25** → **26** → **27** → **23**). For both compounds, the deblock sequence was equally effective if the hydrolysis step (Scheme 4, step b) was omitted, permitting access to both B956 and B957 methyl esters of high purity. The methyl esters are of biological utility as prodrugs of B956 and B957 for cell-based and in vivo experiments.

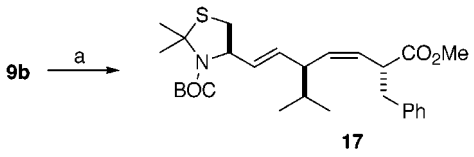
It is difficult to speculate on the basis for the formation of the *Z*-olefin in **11** and **19**. An examination of the solid-state structure of **7a** (Figure 1) reveals that the protons attached to carbon atoms 3 and 4 are gauche aligned, exhibiting a narrow dihedral angle of only 37.9°. Packing forces might be the major factors responsible for this orientation in the solid state. However, its appearance in the solid state predicts that this bent conformation is

Scheme 4[a]



[a] (a) HCl·H_2NMetOMe, NMM, HOBt, 1-[3-(dimethylamino)Propyl]-3-ethylcarbodiimide Hydrochloride, DMF, 100%; (b) LiOH, H_2O, dioxane, 80%; (c) MeO_2CSCl, NaOAc, HOAc, H_2O, DMF, 97%; (d) HCl, EtOAc, 0 °C, 71%; (e) Me_3P, THF, H_2O, TFA, 100%.

Scheme 5[a]



[a] (a) CuCN, BnMgCl, THF, −20 °C to rt, −78 °C, 83%.

at least readily accessible, if not actually favored in the solution phase.

Low-temperature NMR experiments, which freeze out the higher order complexity introduced by the carboxamate rotamers, lend support to a similar conformation being favored in solution. The value of J_{3-4} as measured from the ^{1}H NMR spectrum of **7a** at −60 °C is about 1 Hz while that of J_{4-5}[20] is 8.4 and 9.2 Hz for the two rotamers. That compound **9a** may prefer a similar conformation is indicated by the similarity of its coupling constants when obtained under similar conditions (J_{3-4} = 2.9, 3.8 Hz and J_{4-5} = 10.3, 9.9 Hz, respectively, for the two rotamers). In contrast to **7a** and **9a**, **8a** and **10a** exhibit a different pattern of coupling constants: $J_{3-4} \sim J_{4-5} \sim 1$ Hz for either rotamers of **8a**, while $J_{3-4} \sim 1$ Hz and J_{4-5} = 2.0 Hz for one rotamer of **10a**, and $J_{3-4} = J_{4-5}$ = 4.1 Hz for the other rotamer.

The unexpected stability of these bent conformations potentially rationalize the origin of the surprising ap-

(20) The dihedral angle for H−C4−C5−H from the X-ray structure of **7a** is 182.8°.

pearances of the *Z*-olefinic products. Additionally, it is also possible that this conformation is reinforced in the S_N2' displacement transition state due to stabilization of the incipient positive charge on the mesylate-bearing carbon by electron donation from the $\Delta^{6,7}$ double bond. Such electron donation would tend to reinforce the bent configuration to bring the participating centers into the closest possible proximity.

B956 and B957 were tested in an in vitro enzymatic isoprenyl transferase assays. Both compounds were potent inhibitors of FT (IC_{50}'s of 27 and 19 nM, respectively).[6a,21] As predicted from the previous studies,[12] B957 exhibited a marked 11-fold selectivity for FT over GGT I while B956 was essentially nonselective. This difference in enzyme specificity for two such similar structures has already proven useful in elucidating alternative ras processing pathways in cells.[13a] It is tempting to structurally rationalize this selectivity on the basis of calculated binding interactions with the enzyme. However, the active site of the available FT structure[22] is distorted by the presence of a bound oligopeptide from another molecule of FT and the absence of the FPP cosubstrate. Such calculations must await the release of coordinates derived from more relevant FT structures,[23] and ideally, similar structures of GGT as well.

The present work confirms the accessibility of olefinic peptide mimetics even when operating with synthetically restrictive cysteine-containing peptide leads. Use of the NHK reaction followed by the Yamamoto S_N2' displacement should prove of widespread utility in the preparation of olefinic peptide mimetics of other biologically interesting peptides. Such methodology widens the potential use of olefinic isosteres and increases the possibility of their incorporation into pharmaceuticals of importance.

Experimental Section

General. Starting materials and solvents were purchased from commercial sources and used without further purification unless otherwise noted. Analytical normal phase HPLC was conducted using 5 mm × 10 cm Waters Nova-Pak 6 μM silica column eluting with a linear gradient of 100% hexane to 100% ethyl acetate. Analytical reverse phase HPLC was conducted using a 5 mm × 10 cm Waters Nova-Pak 6 μM HRC18 column eluting with a linear gradient of 0−100% A to B over 30 min (A: 0.15% TFA, 5% MeCN in H_2O; B: 0.15% TFA in MeCN). Preparative reverse phase HPLC was conducted using the analytical reverse phase elution system and either one or two 40 mm × 10 cm Waters 6 μM HRC18 cartridges. All NMR data was collected at either 400 or 500 MHz for proton and 100 or 125 MHz for carbon.

Methyl (2*E*,4*S*)-4-Hydroxy-4-[(5*R*)-*N*-[(*tert*-butyloxy)-carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2-butenoate (2a) and Its (4*R*)-Isomer (3a). At rt, in an N_2-filled drybox, 742 mg (3.03 mmol) aldehyde **1** was dissolved in 31 mL of THF, followed by successive addition of 2.00 g (9.08 mmol) of (2*Z*)-3-iodoacrylate,[16] 1.12 g (9.09 mmol) $CrCl_2$, and 12.5 mg (0.045 mmol) $Ni(COD)_2$. A slight exotherm developed and the reaction mixture changed color from pale green to rusty brown after the addition of the $Ni(COD)_2$. The resulting mixture was stirred for 2 d at which point TLC (25% EtOAc:hexanes) indicated that starting material had been consumed. The reaction mixture was removed from the drybox, quenched by addition of 30 mL of satd NH_4Cl and 30 mL of $CHCl_3$, and then stirred overnight. The aqueous layer was extracted 3 × $CHCl_3$, and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, concentrated, and purified by FC eluting with a stepwise gradient of 25% EtOAc:hexanes to 66% EtOAc:hexanes. A mixture of butenoates **2a** and **3a** (652 mg, 65%) was obtained as an oily white solid.

Data for representative mixture of **2a** and **3a**: ^{1}H NMR ($CDCl_3$) δ: 6.99 bd (J = 14.0 Hz, β), 6.96 dd (J = 5.6, 15.6 Hz, α), 6.17 dd (J = 1.7, 15.5 Hz, β), 6.13 dd (J = 1.0, 15.4 Hz, α), 4.65 s (β), 4.61 t (J = 6.6 Hz, α), 4.50 bs (β), 4.48 t (J = 6.7 Hz, α), 3.75 s (β), 3.74 s (α), 3.15 dd (J = 6.2, 12.4 Hz), 2.91 d (J = 12.3 Hz, β), 2.71 d (J = 12.5 Hz, α), 1.76 s, 1.74 s, 1.44 s.

Separation of alcohols **2a** and **3a** was typically performed as follows: 690 mg (2.08 mmol) of a mixture of **2a** and **3a** was dissolved in 6 mL of CH_2Cl_2 at 0 °C and 548 μL (3.94 mmol) of TEA and 574 μL (2.50 mmol) of TBSOTf were added. The resulting solution was allowed to warm to rt and stirred for 20 min. The CH_2Cl_2 was removed by rotary evaporation and the residue dissolved in EtOAc and washed successively with satd NH_4Cl, satd $NaHCO_3$, and brine. Concentration followed by FC, eluting with 1:10 EtOAc:hexanes, afforded 140 mg of pure **2b**, 130 mg of mixed fractions, and 321 mg of **3b** for a combined recovery of 64%. A typical desilylation was accomplished by stirring a solution of 84 mg of silyl ether **2b** (0.189 mmol), 11 μL HOAc (0.192 mmol), and 386 μL (0.386 mmol) of a 1 M solution of TBAF in THF in 2 mL of THF for 1 h. The THF was removed by rotary evaporation, and the residue was dissolved in EtOAc and washed once with water. The organic layer was dried over Na_2SO_4, filtered, evaporated, and the crude oily residue was purified by FC, eluting with 20% EtOAc:hexanes to afford 45 mg 100% of the pure alcohol diastereomer **2a**.

Data for **2a**: ^{1}H NMR (CD_3OD, −20 °C) δ: 7.01 dd (J = 6.1, 15.5 Hz, major rotamer), 6.97 dd (J = 6.3, 15.3 Hz, minor rotamer), 6.03 dd (J = 1.6, 15.7 Hz, major), 5.93 dd (J = 1.2, 15.7 Hz, minor rotamer), 4.45 m, 4.37 dd (J = 5.1, 8.7 Hz, minor), 4.27 dd (J = 4.9, 9.2, major), 3.73 s (major), 3.68 s (minor), 3.24 dd (J = 5.3, 13.2 Hz), 3.21 dd (J = 5.1, 12.2 Hz), 3.10 dd (J = 11.8 Hz), 3.05 d (J = 13 Hz, minor), 1.80 s (major), 1.78 s (minor), 1.76 s (major), 1.73 s (minor), 1.43 s (minor), 1.41 s (major); ^{13}C NMR (CD_3OD) δ: 168.6, 149.9, 149.8, 120.6, 82.1, 79.5, 71.4, 69.7, 52.1, 52.0, 28.73, 28.66, 27.6; IR (neat) ν cm^{-1}: 3455, 1724, 1696, 1657; $[\alpha]^{20}_D$ = −57.9 (c = 0.00458, $CHCl_3$); LRMS (FAB+) m/z: 354, 276, 254, 232, 216; HRMS calcd for $C_{15}H_{25}NO_5S$ $[M + Na]^+$ 354.1351, found 354.1337.

Data for **3a**: ^{1}H NMR (CD_3OD) δ: 7.18 dd (J = 5.2, 15.6 Hz), 5.98 dd (J = 2.0, 15.5 Hz), 4.72 bm, 4.47 bm, 3.73 s, 3.19 dd (J = 6.7, 12.7 Hz), 2.92 d (J = 13.0 Hz), 1.74 s, 1.73 s, 1.50 s; ^{13}C NMR (CD_3OD) δ: 168.5, 150.9, 121.6, 121.4, 82.2, 73.4, 72.7, 69.6, 69.0, 52.3, 52.2, 52.1, 52.0, 31.4, 30.5, 29.8, 28.7; IR (neat) ν cm^{-1}: 3444, 1726, 1696; $[\alpha]^{20}_D$ = −25.5 (c = 0.0168, $CHCl_3$); LRMS (FAB+) m/z: 354, 276, 232, 216; HRMS calcd for $C_{15}H_{25}NO_5S$ $[M + Na]^+$ 354.1351, found 354.1358.

Data for **2b**: ^{1}H NMR ($CDCl_3$) δ: 7.14 dd (J = 3.7, 15.1 Hz), 5.92 d (J = 15.1 Hz), 4.86 br s, 4.39 br s, 3.73 s, 3.05 dd (J = 7.3, 11.4 Hz), 2.97 m, 1.68−1.71 m, 1.48 s, 0.89 s, 0.097 s, 0.042 s; ^{13}C NMR ($CDCl_3$) δ: 167.6, 149.9, 149.2, 120.0, 81.3, 73.5, 70.8, 69.4, 68.3, 52.19, 52.15, 52.10, 30.9, 29.2, 28.9, 27.0, 26.6, 26.4, 18.7, −3.4, −4.1; IR (neat) ν cm^{-1}: 1727, 1687; $[\alpha]^{20}_D$ = −121.0 (c = 0.0834, $CHCl_3$); LRMS (FAB+) m/z: 468, 346, 216; HRMS calcd for $C_{21}H_{39}NO_5SSi$ $[M + Na]^+$ 468.2216, found 468.2236.

Data for **3b**: ^{1}H NMR ($CDCl_3$) δ: 6.77 br m, 5.71−5.79 br m, 4.29−4.39 br m, 4.14 br m, 3.55 br m, 2.94 dd (J = 5.5, 11.9 Hz), 1.83 br m, 1.57−1.63 br m, 1.27 s, 0.76 s; ^{13}C NMR ($CDCl_3$) δ: 166.0, 152.8, 151.8, 148.9, 120.9, 120.5, 80.2, 72.7, 71.1, 69.6, 68.0, 67.3, 51.1, 51.0, 31.3, 30.4, 29.9, 29.0, 28.7, 28.4, 27.9, 25.5, 25.4, 22.317.7, 13.8, −4.33, −5.04; IR (neat), ν cm^{-1}: 1728, 1694; $[\alpha]^{20}_D$ = −21.6 (c = 0.108, $CHCl_3$); LRMS (FAB+) m/z: 468, 446, 346, 216; HRMS calcd for $C_{21}H_{39}NO_5SSi$ $[M + Na]^+$ 468.2216, found 468.2206.

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Methyl (2*E*,4*S*)-4-(Methansulfonyloxy)-4-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2-butenoate (2c) and Its (4*R*)-Isomer (3c). To a solution of 43 mg alcohol **2a** (0.130 mmol) in 1.5 mL of CH_2Cl_2 cooled to 0 °C was added 33 μL of triethylamine (0.24 mmol) followed by dropwise addition of 17 μL of methanesulfonyl chloride (0.22 mmol). The mixture was stirred for 5 min at 0 °C, the ice bath was removed, and the mixture was stirred an additional 15 min at ambient temperature. CH_2Cl_2 was removed by rotary evaporation and the residue dissolved in EtOAc, washed twice with water, once with brine, dried over Na_2SO_4, filtered, concentrated and purified by FC to afford 53 mg (94%) of the desired mesylate **2c** as an oil. Mesylate **3c** was prepared in an similar manner from alcohol **3a**.

Data for **2c**: ^{1}H NMR (CD_3OD) δ: 6.95 dd (J = 7.7, 15.7 Hz), 6.14 bm, 5.44 t (J = 7.5 Hz), 4.60 bm, 3.74 bs, 3.28 dd (J = 5.5, 13.0 Hz), 3.11 s, 3.00 bd (J = 12.0 Hz). 1.78 bs, 1.76 bs, 1.44 s; ^{13}C NMR (CD_3OD) δ: 166.8, 142.9, 124.4, 79.9, 78.3, 69.8, 67.9, 56.1, 52.5, 39.5, 32.5, 28.9; IR (neat), ν cm^{-1}: 1725, 1692; $[\alpha]^{20}_D$ = − 167 (c = 0.0043, $CHCl_3$); LRMS (FAB+) m/z: 432, 310, 280, 258, 214; HRMS calcd for $C_{16}H_{27}NO_7S_2$ [M + Na]$^+$ 432.1127, found 432.1118.

Data for **3c**: ^{1}H NMR (CD_3OD) δ: 7.12 dd (J = 6.5, 16.0 Hz), 6.08 dd (J = 1.2, 15.7 Hz), 5.59 bm, 4.68 bm, 3.76 s, 3.33 m, 3.14 bs, 2.9 bs, 1.75 s, 1.73 s, 1.52 s; ^{13}C NMR (CD_3OD) δ: 167.3, 143.6, 125.5, 99.5, 82.8, 80.9, 71.5, 67.0, 52.5, 52.4, 39.1, 39.0, 30.9, 30.1, 28.64, 28.59; IR (neat) ν cm^{-1}: 1728, 1694; $[\alpha]^{20}_D$ = −36.3 (c = 0.0199, $CHCl_3$); LRMS (FAB+) m/z: 432, 310, 280, 258; HRMS calcd for $C_{16}H_{27}NO_7S_2$ [M + Na]$^+$, 432.1127, found 432.1132.

Methyl (2*R*/*S*,3*E*)-2-Isopropyl-4-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-3-butenoate (4). A stock solution was prepared as follows: to a suspension of 360 mg (4.0 mmol) CuCN in 40 mL of THF cooled to 0 °C was added dropwise 2.0 mL (4.0 mmol) of a 2 M solution of *i*-PrMgCl in THF. After the addition was complete, the mixture was stirred for an additional 2 h and recooled to −78 °C, and then BF_3OEt_2 (492 μL, 4.0 mmol) was added dropwise. Either mesylate **2c** (50 mg, 0.122 mmol) or **3c** (56 mg, 0.137 mmol) dissolved in 2.0 mL of THF was added to 6 mL of the above stock solution at −78 °C. The resulting mixture was stirred for an additional 30 min at which point TLC (20% ethyl acetate−hexanes) indicated complete disappearance of the starting mesylate. The reactions were quenched with ∼ 3 mL of 1:1 satd NH_4Cl:NH_4OH and the mixture allowed to warm to ambient temperature and stirred overnight. The resulting mixture was extracted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude products were purified by FC eluting with 10% ethyl acetate−hexanes. Diastereomeric mixtures of esters **4** were obtained as clear oils (40 mg, 92%, from **2c**; 43 mg, 88%, from **3c**). Diastereomeric product ratios were most conveniently determined after subsequent reduction. Using analogous conditions on a 22 g scale, a mixture of **2c** and **3c** obtained directly from mesylation of an unseparated mixture of **2a** and **2b** could be converted to **4** in 93% yield.

^{1}H NMR ($CDCl_3$) δ: 5.66 m, 4.78 bm, 3.66 s, 3.25 dd (J = 5.6, 11.6 Hz, (2*S*)-**4**), 3.24 dd (J = 5.9, 11.7 Hz, (2*R*)-**4**), 2.66 m, 2.57 d (J = 11.7 Hz, (2*S*)-**4**), 2.55 d (J = 11.8 Hz, (2*R*)-**4**), 1.96 b sept (J = 6.7 Hz), 1.77 s, 1.74 s, 1.42 s ((2*R*)-**4**), 1.41 s ((2*S*)-**4**), 0.89 d (J = 6.5 Hz, (2*R*)-**4**), 0.87 d (J = 8.0 Hz), 0.85 d (J = 6.5 Hz, (2*S*)-**4**).

(2*R*,3*E*)-2-Isopropyl-4-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-3-butenol (5a) and Its (2*S*)-Isomer (6a). A 1 M solution of DIBAL in hexanes (76 mL, 76 mmol) was added to a solution of 13.6 g (38.0 mmol) of **4** in 250 mL of toluene stirring at room temperature. The reaction mixture was stirred 15 min and then quenched by addition of 250 mL of satd sodium potassium tartrate. The resulting heterogeneous mixture was stirred vigorously for 2 h at room temperature and then diluted with 500 mL ethyl acetate, and the organic layer was separated, washed with brine, dried over Na_2SO_4, filtered through $MgSO_4$, and concentrated. The resulting crude mixture of alcohols was separated and purified by FC, eluting with a 5−25% ethyl acetate−hexanes gradient to afford 8.5 g (68%) of **5a** and 3.6 g 29%) of **6a** (ratio 2.3:1, total yield 97%). Diastereomeric ratios in the crude product could be directly determined by reverse phase HPLC. Compound **4** derived from pure **2c** afforded **5a** and **6a** in a ratio of 2.4:1; for compound **4** derived from pure **3c**, a ratio of 4.4:1 was obtained.

Data for **5a**: ^{1}H NMR ($CDCl_3$) δ: 5.67 dd (J = 6.3, 15.3 Hz), 5.39 dd (J = 9.3, 15.2 Hz), 4.83 bm, 3.65 m, 3.31 t (J = 10.1 Hz), 3.26 dd (J = 6.1, 11.7 Hz), 2.58 (J = 11.7 Hz), 1.99 m, 1.77 bs, 1.74 s, 1.43 s, 0.89 d (J = 6.7 Hz), 0.85 d (J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ: 152.5, 131.3, 80.3, 64.9, 63.8, 51.9, 33.2, 28.6, 28.3, 20.7, 19.4; IR (neat) ν cm^{-1}: 3452, 1692; $[\alpha]^{20}_D$ = −64.4 (c = 0.0854, $CHCl_3$); LRMS (FAB+) m/z: 352, 330, 274, 230; HRMS calcd for $C_{17}H_{31}NO_3S$ [M + Na]$^+$ 352.1922, found 352.1941.

Data for **6a**: ^{1}H NMR ($CDCl_3$) δ: 5.62 dd (J = 7.1, 15.2 Hz), 5.33 m, 4.73 bm, 3.64 dt (J = 5.4, 15.2 Hz), 3.32 t (J = 10.4 Hz), 3.36 dd (J = 6.2, 11.8 Hz), 1.98 m, 1.73 bs, 1.43 s, 0.88 d (J = 6.7), 0.84 d (J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ: 133.3, 80.4, 80.0, 63.7, 52.6, 33.1, 30.0, 29.6, 28.8, 28.4, 20.7, 20.1; IR (neat) ν cm^{-1}: 3443, 1693; $[\alpha]^{20}_D$ = −62.8 (c = 0.00916, $CHCl_3$); LRMS (FAB+) m/z: 352, 330, 274, 230; HRMS calcd for $C_{17}H_{31}NO_3S$ [M + Na]$^+$ 352.1922, found 352.1915.

(2*R*,3*E*)-2-Isopropyl-4-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-3-butenal (5b). A solution of 659 μL (7.55 mmol) of oxalyl chloride in 30 mL of CH_2Cl_2 was cooled to −60 °C and 1.15 mL (16.2 mmol) of DMSO added dropwise. A solution of 1.77 g (5.39 mmol) of **5a** in 20 mL of CH_2Cl_2 was added dropwise and the reaction mixture allowed to stir for 10 min after the addition was completed at which point the mixture had become cloudy. TEA (3.00 mL, 21.57 mmol) was added dropwise and the mixture warmed to rt. The reaction became homogeneous after the TEA had been completely added, but became cloudy again upon warming to rt. Satd NH_4Cl (50 mL) was added, the resulting two-phase mixture was extracted with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4, filtered, and concentrated to 1.9 g of a yellow oil. After purification by FC, eluting with 1:10 EtOAc: hexanes, 1.60 g (91%) of **5b** was obtained as a clear oil.

^{1}H NMR ($CDCl_3$) δ: 9.58 d (J = 2.8 Hz), 5.75 dd (J = 7.1, 15.3 Hz), 5.61 bm, 4.84 bm, 3.27 dd (J = 6.1, 11.8 Hz), 2.72 bm, 2.57 d (J = 11.8 Hz), 2.13 m, 1.76 s, 1.44 s, 0.95 d (J = 6.6 Hz), 0.91 d (J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ: 202.3, 152.4, 135.6, 125.5, 80.3, 65.1, 63.0, 33.5, 29.9, 28.6, 28.5, 28.4, 20.9, 19.5; IR (neat) ν cm^{-1}: 1726, 1692; $[\alpha]^{20}_D$ = − 86.1 (c = 0.0544, $CHCl_3$); LRMS (FAB+) m/z: 681, 350, 321, 294, 228; HRMS calcd for $C_{17}H_{29}NO_3S$ [M + Na]$^+$ 350.1766, found 352.1781.

(2*R*,3*E*)-2-Isopropyl-4-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-3-butenal (6b). Using the above conditions for the conversion of **5a** to **5b**, 2.04 g (6.19 mmol) of **6a** was oxidized to yield 1.93 g (95%) of **6b**. ^{1}H NMR ($CDCl_3$) δ: 9.57 d (J = 2.8 Hz), 5.75 dd (J = 6.8, 15.5 Hz), 5.58 bm, 4.82 bm, 3.28 dd (J = 6.2, 11.8 Hz), 2.72 m, 2.58 d (J = 11.8 Hz), 2.12 m, 1.78 bs, 1.75 s, 0.95 d (J = 6.7 Hz), 0.89 d (J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ: 201.7, 152.2, 135.0, 125.3, 80.1, 65.0, 62.3, 33.2, 30.5, 29.9, 29.2, 28.4, 28.3, 20.7, 19.3; IR (neat) ν cm^{-1}: 1726, 1693; $[\alpha]^{20}_D$ = −19.5 (c = 0.0495, $CHCl_3$); LRMS (FAB+) m/z: 681, 350, 321, 294, 228, 176, 154; HRMS calcd for $C_{17}H_{29}NO_3S$ [M + Na]$^+$ 350.1766, found 350.1764.

Methyl (2*E*,4*R*,5*R*,6*E*)-4-Hydroxy-5-isopropyl-7-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2,6-heptadienoate (7a) and Its (5*S*) Isomer (9a). In an N_2-filled drybox, 2.10 g (17.08 mmol) of chromium dichloride was added to a solution of 1.60 g (4.88 mmol) of **5b** and 3.10 g (14.64 mmol) of (2*Z*)-3-iodoacrylate in 50 mL of THF followed by addition of 20 mg (0.073 mmol) of Ni(COD)$_2$ in one portion. After stirring overnight, the reaction was removed from the drybox and the THF removed under reduced pressure. The residue was dissolved in a mixture of 35 mL of satd aq NH_4Cl, 35 mL of $CHCl_3$, and 5 mL of 10% aq $Na_2S_2O_3$, and stirred for 1 h, and then the $CHCl_3$ layer was separated. The $CHCl_3$ layer was washed further by stirring with satd aq NH_4Cl and 10% aq $Na_2S_2O_3$ an additional two times. The aqueous layers were combined and back extracted with $CHCl_3$. The $CHCl_3$ extracts

were combined, washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure to afford 3.95 g of a green oily residue. The residue was chromatographed over silica gel eluting with 1:3 ethyl acetate:hexanes to afford 1.60 g (79%) of a 5.5:1 mixture of **7a** and **9a** as a yellow oil. The ratio was determined by HPLC analysis on a C18 column eluting with a gradient of 0−100% (phase A: 0.15% TFA, 5% MeCN in H2O; phase B: 0.15% TFA in MeCN).

Data for **7a**: ^{1}H NMR ($CDCl_3$) δ: 6.98 dd (J = 4.7, 15.6 Hz), 6.02 dd (J = 0.9, 15.6 Hz), 5.71 dd (J = 6.4, 15.3 Hz), 5.31 m, 4.82 br s, 4.40 t (J = 4.6 Hz), 3.71 s, 3.26 dd (J = 6.1, 11.8 Hz), 2.55 d (J = 11.7 Hz), 2.02 m, 1.74 br s, 1.43 br s, 0.95 d (J = 6.6 Hz), 0.88 d (J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ: 166.7, 148.0, 129.1, 121.2, 70.6, 56.2, 51.6, 50.1, 50.0, 49.8, 28.4, 28.2, 20.7; IR (neat) ν cm^{-1}: 3460, 1725, 1692; $[\alpha]^{20}_D = -71.1$ (c = 0.0662, $CHCl_3$); LRMS (FAB+) m/z: 436, 388, 314, 160, 109; HRMS calcd for $C_{21}H_{35}NO_5S$ [M + Na]$^+$ 436.2134, found 436.2138.

Data for **9a**: ^{1}H NMR ($CDCl_3$) δ: 7.06 dd (J = 4.1, 15.6 Hz), 6.11 d (J = 15.5 Hz), 5.59 dd (J = 6.3, 15.1 Hz), 5.21 br s, 4.65−4.85 br m, 4.41 s, 3.72 s, 3.21br s, 2.64 br s, 2.57 m, 2.05 m, 1.72 br s, 1.45 br s, 0.98 d (J = 6.5 Hz), 0.86 br d (J = 3.9 Hz); ^{13}C NMR ($CDCl_3$) δ: 166.8, 147.8, 135.2, 130.2, 121.5, 70.3, 66.5, 56.7, 51.56, 51.53, 51.47, 51.44, 33.0, 30.2, 29.7, 28.4, 28.3, 21.4, 20.5; IR (neat) ν cm^{-1}: 3468, 1725, 1693; $[\alpha]^{20}_D$ = −4.53 (c = 0.0269, $CHCl_3$); LRMS (FAB+) m/z: 436, 346, 314, 217, 176; HRMS calcd for $C_{21}H_{35}NO_5S$ [M + Na]$^+$ 436.2134, found 436.2114.

Methyl (2*E*,4*S*,5*R*,6*E*)-4-Hydroxy-5-isopropyl-7-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2,6-heptadienoate (8a). A suspension of the Dess−Martin reagent[24] (155 mg, 0.370 mmol), molecular sieves 4 Å (37 mg), and *tert*-butyl alcohol (27 mg, 0.370 mmol) in CH_2Cl_2 (1.2 mL) was stirred at room temperature for 0.5 h. To this suspension was added a solution of **7a** (51 mg, 0.123 mmol) in CH_2Cl_2 (0.8 mL) and the mixture stirred at room temperature for 15 min. After dilution with 50 mL of ethyl ether, the solid was removed by centrifugation. The supernatant was then washed with aq sodium thiosulfate, aq sodium bicarbonate, and brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was chromatographed on silica gel (eluting with 1:10 ethyl acetate:hexane) to afford the intermediate ketone as a yellow oil (22 mg, 43%).

This oil (22 mg, 0.054 mmol) was dissolved in methanol (1 mL), cooled to 0 °C, and 2 mg (0.053 mmol) of sodium borohydride was added. The solution was stirred for 0.5 h and then concentrated under reduced pressure, and the resulting residue was dissolved in ethyl acetate. The solution was washed with 0.1 N HCl, water, and brine and then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluting with 1:2 ethyl acetate:hexanes) to yield a colorless oil (20 mg, 91%), which was a mixture of two diastereomers (1:1). The two diastereomers were separated by reverse phase HPLC to afford the starting diastereomer **7a** and a new compound **8a**.

Data for **8a**: ^{1}H NMR ($CDCl_3$) δ: 6.93 dd (J = 5.3, 15.6 Hz), 6.06 (d, J = 15.7 Hz), 5.66 (dd, J = 6.2 15.4 Hz), 5.47 (dd, J = 10.1, 15.0 Hz). 4.82 br s, 4.29 br s, 3.73 s, 3.26 (dd, J = 6.2, 11.8 Hz), 2.57 m, 1.80−1.96 m, 1.75 br s, 1.44 br s, 0.80−0.97 m; ^{13}C NMR (CD_3OD) δ: 168.8, 154.2, 72.2, 56.7, 52.2, 29.7, 28.9, 27.5; IR (neat) ν cm^{-1}: 1724, 1691; $[\alpha]^{20}_D = -51.6$ (c = 0.0058, $CHCl_3$); LRMS (FAB+) m/z: 436, 406, 314, 217, 176; HRMS calcd for $C_{21}H_{35}NO_5S$ [M + Na]$^+$ 436.2134, found 436.2118.

Methyl (2*E*,4*R*,5*S*,6*E*)-4-Hydroxy-5-isopropyl-7-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2,6-heptadienoate (9a) and Its (4*S*) Isomer (10a). NHK reaction of **6b** with (2*Z*)-3-iodoacrylate was performed using a procedure similar to that used to prepare **7a** and **9a** from **5b** above. From 1.556 g of **6b** (4.76 mmol) was obtained a 1.345 g mixture of two isomers, **9a** and **10a**, in 68% yield in a ratio of 1.4:1 as determined by analytical reverse phase HPLC. Data for **9a** are identical to that reported above.

Data for **10a**: ^{1}H NMR ($CDCl_3$) δ: 6.93 dd (J = 5.5, 15.7 Hz), 6.05 dd (J = 1.1, 15.5 Hz), 5.65 dd (J = 7.0, 15.2 Hz), 5.51 m, 4.73 br s, 4.21 (t, J = 6.2 Hz), 3.72 s, 3.25 dd (J = 6.2, 11.9 Hz), 2.50−2.80 m, 1.93 m, 1.73 br s, 1.45 br s, 0.87 m; ^{13}C NMR ($CDCl_3$) δ: 166.8, 148.8, 121.1, 71.1, 55.5, 51.53, 51.49, 29.6, 28.4, 28.3, 27.8, 21.9; IR (neat) ν cm^{-1}: 3474, 1725, 1693; $[\alpha]^{20}_D = -57.0$ (c = 0.025, $CHCl_3$); LRMS (FAB+) m/z: 436, 314; HRMS calcd for $C_{21}H_{35}NO_5S$ [M + Na]$^+$ 436.2134, found 436.2148.

Methyl (2*E*,4*R*,5*R*,6*E*)-4-(Mesyloxy)-5-isopropyl-7-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2,6-heptadienoate (7b). Triethylamine (22 mg, 0.218 mmol) was added to a solution of **7a** (30 mg, 0.0726 mmol) in 0.82 mL of CH_2Cl_2 cooled to 0 °C, followed by the dropwise addition of 11.3 of μL methansulfonyl chloride (16.7 mg, 0.145 mmol). The reaction mixture was stirred at 0 °C for 40 min and then quenched by addition of a solution of satd aq ammonium chloride. The mixture was extracted twice with CH_2Cl_2, the combined extracts were washed with water and brine, dried over anhydrous sodium sulfate, and the solvent was concentrated under reduced pressure. The residue was chromatographed over 4 g of silica gel (eluting with 1:3.3 ethyl acetate:hexanes) to provide 27 mg (77%) **7b** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 6.82 dd (J = 6.6, 15.7 Hz), 6.06 d (J = 15.6 Hz), 5.71 dd (J = 7.3, 15.2 Hz), 5.32 br s, 5.24 t (J = 6.8 Hz), 4.81 br s, 3.73 s, 3.24 dd (J = 6.0, 11.7 Hz), 2.99 s, 2.51 d (J = 11.7 Hz), 2.25 dd (J = 7.3, 15.8 Hz), 1.87 oct (J = 6.5 Hz), 1.74 s, 1.43 s, 0.93 d (J = 6.3 Hz), 0.89 d (J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ: 166.4, 152.9, 143.9, 142.9, 124.8, 124.6, 81.7, 81.1, 80.8, 65.7, 54.9, 54.4, 52.6, 40.0, 33.5, 32.3, 31.4, 30.6, 29.6, 29.1, 28.8, 28.4, 23.4, 21.8, 21.7, 18.9, 14.8; IR (neat) ν cm^{-1}: 1727, 1690; $[\alpha]^{20}_D = -56.0$ (c = 0.0223, $CHCl_3$); LRMS (FAB+) m/z: 514, 418, 362, 340, 296; HRMS calcd for $C_{22}H_{37}NO_7S2$ [M + Na]$^+$ 514.1909, found 514.1916.

Methyl (2*E*,4*S*,5*S*,6*E*)-4-(Mesyloxy)-5-isopropyl-7-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2,6-heptadienoate (9b). Alcohol **9a** (12 mg, 0.0291 mmol) was converted to mesylate **9b** in 86% yield using the same procedure as described above for the conversion of **7a** to **7b**. ^{1}H NMR ($CDCl_3$) δ: 6.84 dd (J = 6.7, 15.7 Hz), 6.08 d (J = 15.8 Hz), 5.61 dd (J = 5.5, 15.2 Hz), 5.29 br s, 5.22 t (J = 6.7 Hz), 4.83 br s, 3.72 s, 3.24 dd (J = 6.3, 11.8 Hz), 2.98 s, 2.50 d (J = 11.8 Hz), 2.29 dd (J = 8.6, 14.4 Hz), 1.91 oct (J = 6.6 Hz), 1.73 s, 1.43 s, 0.93 d (J = 6.2 Hz), 0.89 d (J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ: 166.4, 152.9, 143.0, 136.6, 135.5, 126.7, 125.9, 124.9, 81.0, 65.6, 64.7, 54.2, 52.5, 40.0, 34.1, 33.5, 32.3, 31.4, 30.1, 29.2, 29.1, 28.9, 28.8, 28.2, 23.3, 21.7, 18.5, 14.8; IR (neat) ν cm^{-1}: 1727, 1690; $[\alpha]^{20}_D = -34.9$ (c = 0.0621, $CHCl_3$); LRMS (FAB+) m/z: 514, 418, 362, 261, 217; HRMS calcd for $C_{22}H_{37}NO_7S_2$ [M + Na]$^+$ 514.1909, found 514.1906.

Methyl (2*S*,3*Z*,5*S*,6*E*)-2-(Phenylmethyl)-5-isopropyl-7-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2,6-heptadienoate (11) and Its (2R,3*E*,5S,6*E*) Isomer (14). Using a procedure similar to the procedure for the preparation of **17** from **9b**, a mixture of **11** and **14** (25 mg, 89%, ratio 2.6:1) was obtained from S_N2' displacement reaction of 28 mg of **7b** (0.057 mmol). Separation of **11** and **14** was performed by chromatography over silica gel (eluting with 1:20 ethyl acetate:hexanes).

Data for **11**: ^{1}H NMR ($CDCl_3$) δ: 7.22−7.26 m, 7.12−7.18 m, 5.37−5.49 m, 4.70 br s, 3.57−3.64 m, 3.59 s, 3.20 dd (J = 6.0, 11.6 Hz), 3.02 dd (J = 8.0, 13.6 Hz), 2.74 dd (J = 6.8, 13.6 Hz), 2.68 dd (J = 7.4, 9.0 Hz), 2.42 d (J = 11.6 Hz), 1.74−1.77 m, 1.49−1.58 m, 1.42 s, 0.85 d (J = 6.5 Hz), 0.81 d (J = 6.7 Hz); ^{13}C NMR (CD_3OD) δ: 175.8, 154.1, 140.2, 135.5, 135.1, 134.6, 130.1, 129.6, 129.5, 128.6, 128.3, 127.7, 127.6, 66.8, 52.5, 52.4, 52.3, 52.2, 48.0, 47.8, 40.1, 34.4, 33.8, 30.2, 29.0, 28.9, 20.9, 20.7, 20.5; IR (neat) ν cm^{-1}: 1738, 1694; $[\alpha]^{20}_D = +17.6$ (c = 0.0647, $CHCl_3$); LRMS (FAB+) m/z: 510, 388, 217; HRMS calcd for $C_{28}H_{41}NO_4S$ [M + Na]$^+$ 510.2654, found 510.2673.

Data for **14**: ^{1}H NMR ($CDCl_3$) δ: 7.22−7.25 m, 7.11−7.18 m, 5.42−5.52 m, 5.38−5.40 m, 4.70 br s, 3.61 s, 3.23−3.31 m,

(24) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899. (c) Meyer, S. D.; Schreiber, S. L. *Ibid.* **1994**, *59*, 7549.

3.05 dd (J = 7.7, 13.6 Hz), 2.78 dd (J = 7.4, 13.6 Hz), 2.53 d (J = 11.6 Hz), 2.39−2.41 m, 1.75−1.77 m, 1.50−1.58 m, 1.43 s, 0.77 d (J = 6.7 Hz); ^{13}C NMR (CD3OD) δ: 175.7, 153.9, 140.13, 140.09, 136.8, 134.1, 130.2, 129.5, 129.4, 128.8, 128.2, 127.5, 79.6, 66.7, 53.7, 52.5, 52.4, 52.35, 52.29, 39.9, 34.4, 33.6, 29.04, 28.99, 20.9, 20.7, 20.5; IR (neat) ν cm^{-1}: 1738, 1693; $[\alpha]^{20}_D$ = − 67.8 (c = 0.0979, $CHCl_3$); LRMS (FAB+) m/z: 510, 388; HRMS calcd for $C_{28}H_{41}NO_4S$ [M + Na]$^+$ 510.2654, found 510.2668.

(2*S*,3*Z*,5*S*,6*E*)-2-(Phenylmethyl)-5-isopropyl-7-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2,6-heptadienoic acid (12) and Its (2*R*,3*Z*,5*S*,6*E*) Isomer (13). A 2.0 M aqueous solution of lithium hydroxide (0.28 mL, 0.56 mmol) was added to a solution of 27 mg of **11** (0.055 mmol) in 0.28 mL of dioxane. The mixture was stirred at rt for 23 h, acidified with 0.6 mL of 1 N HCl (0.6 mmol), and then extracted with ethyl acetate three times. The combined extracts were washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to yield 22 mg of a colorless oil (85%), which is a mixture of **12** and **13** in the ratio of 27:1 as determined by reverse phase HPLC. The separation of the two epimers could be accomplished by preparative reverse phase HPLC using similar conditions.

Data for **12**: ^{1}H NMR (CD_3OD) δ: 7.21−7.25 m, 7.13−7.18 m, 5.38−5.51 m, 4.71 br s, 3.54−3.60 m, 3.25 dd (J = 6.0, 11.8 Hz), 3.00 dd (J = 7.8, 13.5 Hz), 2.72 dd (J = 6.9, 13.4 Hz), 2.45 d (J = 11.7 Hz), 1.73−1.76 m, 1.51−1.66 m, 1.43 s, 0.89 d (J = 6.6 Hz), 0.85 d (J = 6.7 Hz); ^{13}C NMR (CD_3OD) δ: 177.5, 154.1, 140.4, 135.1, 130.2, 129.5, 128.7, 127.5, 48.2, 40.2, 33.9, 32.9, 28.92, 28.87, 23.8, 20.7, 14.6; IR (neat) ν cm^{-1}: 1734, 1694; $[\alpha]^{20}_D$ = +24.0 (c = 0.0101, $CHCl_3$); LRMS (FAB+) m/z: 496, 374; HRMS calcd for $C_{27}H_{39}NO_4S$ [M + Na]$^+$ 496.2498, found 496.2501.

Data for **13**: ^{1}H NMR (CD_3OD) δ: 7.22−7.26 m, 7.13−7.19 m, 5.58 dd (J = 7.0, 15.3 Hz), 5.35−5.47 m, 4.73 t (J = 6.4 Hz), 3.53−3.59 m, 3.25 dd (J = 6.0, 11.7 Hz), 3.06 dd, (J = 6.4, 13.3 Hz), 2.73 dd (J = 8.3, 13.3 Hz), 2.52−2.58 m, 1.73−1.75 m, 1.41 s, 1.25−1.34 m, 0.75 d (J = 6.6 Hz), 0.60 d (J = 6.8 Hz); ^{13}C NMR (CD_3OD) δ: 177.4, 154.1, 140.5, 135.3, 134.4, 130.4, 130.3, 129.5, 128.6, 127.6, 81.3, 66.9, 48.1, 40.3, 34.2, 33.5, 28.91, 28.85, 20.7; IR (neat) ν cm^{-1}: 1693; $[\alpha]^{20}_D$ = −26.5 (c = 0.0173, $CHCl_3$); LRMS (FAB+) m/z: 496, 374; HRMS calcd for $C_{27}H_{39}NO_4S$ [M + Na]$^+$ 496.2498, found 496.2496.

(2*R*,3*E*,5*S*,6*E*)-2-(Phenylmethyl)-5-isopropyl-7-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2,6-heptadienoic Acid (15) and Its (2*S*,3*E*,5*S*,6*E*) Isomer (16). Methyl ester **14** (2.847 g, 5.846 mmol) was hydrolyzed as for **11** above to afford a mixture of **15** and **16** in a ratio of 1:1. The separation of a 276 mg portion of the crude product by reverse phase HPLC afforded pure **15** (92 mg, 33%) and **16** (145 mg, 53%) and the remaining material in mixed fractions.

Data for **15**: ^{1}H NMR (CD_3OD) δ: 7.21−7.24 m, 7.13−7.16 m, 5.41−5.48 m, 4.78 br s, 3.22−3.32 m, 3.03 dd (J = 7.4, 13.6 Hz), 2.76 dd (J = 7.7, 13.5 Hz), 2.55 d (J = 11.8 Hz), 2.43−2.44 m, 1.75−1.76 m, 1.54 (oct, J = 6.7 Hz), 1.45 s, 0.81 d (J = 6.7 Hz), 0.79 d (J = 6.3 Hz); ^{13}C NMR (CD_3OD) δ: 177.6, 154.1, 140.5, 136.6, 134.3, 130.4, 130.3, 129.5, 129.4, 129.3, 127.5, 53.79, 53.84, 52.7, 40.0, 33.7, 29.04, 28.98, 20.9, 20.6; IR (neat) ν cm^{-1}: 1735, 1706, 1694; $[\alpha]^{20}_D$ = −83.1 (c = 0.0637, $CHCl_3$). LRMS (FAB+) m/z: 496, 374; HRMS calcd for $C_{27}H_{39}NO_4S$ [M + Na]$^+$ 496.2498, found 496.2502.

Data for **16**: ^{1}H NMR (CD_3OD) δ: 7.21−7.25 m, 7.14−7.19 m, 5.37−5.56 m, 4.79 br s, 3.24−3.29 m, 3.05 dd (J = 7.3, 13.7 Hz), 2.77 dd (J = 8.2, 13.7 Hz), 2.56 d (J = 11.4 Hz), 2.42 q (J = 7.3 Hz), 1.77 s, 1.75 s,, 1.52 oct (J = 6.9 Hz), 1.44 s, 0.78 d (J = 6.9 Hz), 0.73 d (J = 6.9 Hz); ^{13}C NMR (CD_3OD) δ: 177.7, 154.2, 140.4, 136.5, 130.4, 130.3, 129.52, 129.48, 129.45, 129.24, 52.84, 40.1, 33.7, 29.0, 28.9, 20.8, 20.6; IR (neat) ν cm^{-1}: 1733, 1696; $[\alpha]^{20}_D$ = −10.2 (c = 0.112, $CHCl_3$). LRMS (FAB+) m/z: 496, 374; HRMS calcd for $C_{27}H_{39}NO_4S$ [M + Na]$^+$ 496.2498, found 496.2515.

Methyl (2*S*,3*Z*,5*R*,6*E*)-2-(Phenylmethyl)-5-isopropyl-7-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2,6-heptadienoate (17). A 2.0 M solution of benzylmagnesium chloride (0.122 mL, 0.244 mmol) was added dropwise to a suspension of 22.0 mg of CuCN (0.244 mmol) in 1.2 mL of THF maintained under Ar atmosphere at − 20 °C. After the addition was completed, the solution was gradually warmed to rt and the color changed to dark brown at which point it was cooled to −78 °C and 36 μL of BF_3OEt_2 (0.293 mol) was added. Next, a solution of 12 mg **9b** (0.0244 mmol) in 0.2 mL THF was added and the resulting mixture was stirred for 20 min at −78 °C. The reaction was then quenched by addition of a 2:1 solution of satd ammonium chloride and ammonium hydroxide, warmed to room temperature, stirred for 15 min, and then extracted three times with ethyl acetate. The extracts were combined, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was chromatographed over silica, eluting with 1:20 ethyl acetate:hexanes to afford 10 mg **17** (83%) as a colorless oil. Compound **17** was contaminated with a chromatographically inseparable related impurity to the extent of 10−20% as estimated from the ^{1}H NMR spectrum. This ratio was determined to be 6.8:1 by DIBAL reduction of the mixture and subsequent analysis by RP-HPLC. The impurity was tentatively assigned the structure of the C.1 epimer on the basis of the ^{1}H NMR data. ^{1}H NMR (CD_3OD) δ: 7.22−7.26 m, 7.12−7.19 m, 5.31−5.56 m, 4.79 br s, 3.25−3.41 m, 3.05 dd (J = 7.1, 13.5 Hz), 2.77 dd (J = 7.8, 13.7 Hz), 2.57 d (J = 11.9 Hz), 2.41 q (J = 7.1 Hz), 1.75−1.79 m, 0.78 d (J = 6.9 Hz), 0.73 d (J = 6.4 Hz); ^{13}C NMR (CD_3OD) δ: 174.8, 153.0, 139.5, 134.4, 134.0, 129.7, 129.6, 129.0, 128.5, 127.8, 127.1, 127.0, 65.9, 52.3, 51.9, 48.1, 47.2, 39.6, 39.5, 34.2, 33.1, 32.9, 29.2, 29.1, 20.9, 20.6, 20.4; IR (neat) ν cm^{-1}: 1738, 1693; $[\alpha]^{20}_D$ = −149 (c = 0.0517, $CHCl_3$); LRMS (FAB+) m/z: 510, 388, 217; HRMS calcd for $C_{28}H_{41}NO_4S$ [M + Na]$^+$ 510.2654, found 510.2649.

Methyl (2*S*,3*Z*,5*S*,6*E*)-2-(Phenylmethyl)-5-isopropyl-7-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2,6-heptadienyl Methionine (18). 4-Methylmorpholine (47 μL, 0.427 mmol) is added to a DMF (2.5 mL) solution containing 126 mg of **12** (0.267 mmol), 80 mg of methionine methyl ester hydrochloride (0.400 mmol), 58 mg of 1-hydroxybenzotriazole hydrate (0.427 mmol), and 103 mg of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.534 mmol). The mixture was stirred at room temperature for 16 h, diluted with 50 mL of ethyl acetate, and washed with 2 × 50 mL of water and once with brine. The solvent was removed under reduced pressure, and the residue was chromatographed over silica, eluting with 1:4 ethyl acetate: hexanes to afford 165 mg of **18** as a colorless oil (100%). ^{1}H NMR (CD_3OD) δ: 8.25 d (J = 8.2 Hz), 7.21−7.26 m, 7.16−7.18 m, 5.67 dd (J = 7.0, 15.2 Hz), 5.38−5.59 m, 4.79 br s, 4.46 m, 3.64 s, 3.60 m, 3.30 m, 2.90−2.94 m, 2.68 dd (J = 5.2, 13.3 Hz), 2.52 d (J = 11.8 Hz), 1.97 s, 1.83−2.06 m, 1.75−1.78 m, 1.64−1.72 m, 1.58 oct (J = 7.0), 1.44 s, 0.93 d (J = 6.3 Hz), 0.89 d (J = 6.6 Hz); ^{13}C NMR (CD_3OD) δ: 176.0, 175.9, 173.6, 173.5, 154.1, 140.4, 135.2, 134.3, 130.34, 130.26, 129.57, 127.6, 52.9, 52.84, 52.75, 52.68, 52.36, 52.26, 40.9, 34.5, 33.7, 32.0, 30.8, 30.3, 29.0, 28.9, 20.8, 15.4, 15.2; IR (neat) ν cm^{-1}: 1743, 1691; $[\alpha]^{20}_D$ = +51.6 (c = 0.0452, $CHCl_3$); LRMS (FAB+) m/z: 642, 520; HRMS calcd for $C_{33}H_{50}N_2O_5S_2$ [M + Na]$^+$ 641.3059, found 641.3058.

(2*S*,3*Z*,5*S*,6*E*)-2-Phenylmethyl-5-isopropyl-7-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2,6-heptadienyl methionine (19). A 1 M solution of lithium hydroxide (1.0 mL, 1.0 mmol) was added to a solution of 50 mg of **17** (0.081 mmol) in 1.0 mL of dioxane. The mixture was stirred at room temperature for 1 h and then acidified by addition of 1 N hydrochloric acid. The mixture was extracted with ethyl acetate and then washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by reverse phase HPLC to yield 39 mg of **19** as a colorless oil (80%). ^{1}H NMR (CD_3OD) δ: 8.11 d (J = 8.2 Hz), 7.23−7.27 m, 7.15−7.19 m, 5.67 dd (J = 15.1, 6.9 Hz), 5.59 t (J = 10.5 Hz), 5.50−5.54 br m, 5.42 t (J = 10.5 Hz), 4.79 br m, 4.43 dd (J = 9.2, 4.1 Hz), 3.62 dt (J = 5.0, 10.1 Hz), 3.29 dd (J = 11.9, 6.0 Hz), 2.92 m, 2.70 dd (J = 13.3, 5.5 Hz), 2.52 d (J = 11.4 Hz), 1.99−2.08 m, 1.98 s, 1.84−1.98 m,

1.76−1.79 m, 1.66−1.75 m, 1.58 oct (J = 6.9), 1.45 s, 0.93 d (J = 6.4 Hz), 0.89 d (J = 6.9 Hz); ^{13}C NMR (CD_3OD) δ: 176.08, 175.99, 174.8, 154.1, 140.5, 135.2, 134.4, 130.4, 130.3, 129.6, 127.6, 81.3, 66.8, 52.4, 52.3, 40.9, 34.5, 33.8, 32.3, 30.9, 30.1, 29.0, 28.9, 20.8, 15.2; IR (neat) ν cm^{-1}: 1734, 1691, 1653; $[\alpha]^{20}_D$ = +43.9 (c = 0.0368, $CHCl_3$); LRMS (FAB+) m/z: 642, 520; HRMS calcd for $C_{32}H_{48}N_2O_5S_2$ [M + Na]$^+$ 627.2902, found 627.2907.

(2*S*,3*Z*,5*S*,6*E*,8*R*)-2-(Phenylmethyl)-5-isopropyl-8-(*tert*-butyloxycarbonylamino)-9-(carbomethoxysulfenylthio)-2,6-nonadienyl Methionine (20). To a solution of 38 mg of **19** (0.063 mmol) and 17 mg of sodium acetate hydrate (0.125 mmol) in 0.6 mL of a 8:1:0.5 mixture of acetic acid:DMF:water at 0 °C was added 12 mg of methoxycarbonylsulfenyl chloride (0.094 mmol). The solution was stirred for 15 min during which period it was allowed to warm to room temperature. The solution was concentrated under vacuum, and the residue was chromatographed using reverse phase HPLC to yield 40 mg **20** as a colorless oil (97%). ^{1}H NMR (CD_3OD) δ: 8.09 d (J = 8.2 Hz), 7.22−7.27 m, 7.15−7.19 m, 5.58 t (J = 10.1 Hz), 5.55 m, 5.41 t (J = 10.5 Hz), 5.34 dd (J = 15.1, 6.4 Hz), 4.43−4.47 m, 4.24 br q (J = 6.4 Hz), 3.88 s, 3.57 m, 2.84−2.96 m, 2.73 dd (J = 13.3, 6.0 Hz), 2.00−2.13 m, 2.00 s, 1.91−1.99 m, 1.69−1.77 m, 1.59 oct (J = 6.9 Hz), 1.43 s, 0.90 d (J = 6.9 Hz), 0.87 d (J = 6.9 Hz); ^{13}C NMR (CD_3OD) δ: 176.1, 174.8, 171.4, 157.6, 140.5, 135.5, 134.0, 130.4, 130.3, 129.8, 129.6, 129.5, 127.6, 80.4, 56.3, 56.2, 53.1, 52.4, 52.4, 45.4, 40.9, 33.7, 32.3, 31.0, 28.92, 28.88, 20.8, 20.6, 15.2; IR (neat) ν cm^{-1}: 1733, 1654; $[\alpha]^{20}_D$ = +92.4 (c = 0.0343, $CHCl_3$); LRMS (FAB+) m/z: 677, 599, 440; HRMS calcd for $C_{31}H_{46}N_2O_7S_3$ [M + Na]$^+$ 677.2365, found 677.2359.

(2*S*,3*Z*,5*S*,6*E*,8*R*)-2-(Phenylmethyl)-5-isopropyl-8-amino-9-(carbomethoxysulfenylthio)-2,6-nonadienyl methionine (21). Dry HCl gas was bubbled for 1 min through a solution of 40 mg of **20** (0.061 mmol) in 10 mL of ethyl acetate maintained at 0 °C. The solution was stirred for 15 min further, during which period it was allowed to warm to the room temperature and then concentrated under reduced pressure. The residue was purified by reverse phase HPLC to afford 29 mg of the trifluoroacetate salt **21**, obtained as a colorless oil (71%). ^{1}H NMR (CD_3OD) δ: 8.10 d (J = 8.2 Hz), 7.26−7.29 m, 7.17−7.20 m, 5.85 dd (J = 15.6, 7.8 Hz), 5.66 t (J = 10.5 Hz), 5.38−5.44 m, 4.44−4.48 m, 3.88−3.94 m, 3.93 s, 3.59 td (J = 9.6, 6.4 Hz), 3.06 d (J = 6.9 Hz), 2.94−3.00 m, 2.73 dd (J = 13.3, 6.0 Hz), 2.01−2.15 m, 2.00 s, 1.92−1.99 m, 1.70−1.78 m, 1.66 oct (J = 6.9), 0.94 d (J = 6.9 Hz), 0.90 d (J = 6.4 Hz); ^{13}C NMR (CD_3OD) δ: 176.0, 175.9, 174.8, 171.7, 141.6, 140.4, 133.0, 130.5, 130.3, 129.7, 129.6, 127.7, 124.7, 57.0, 56.8, 53.4, 53.3, 52.5, 52.4, 43.2, 41.1, 33.6, 32.3, 31.0, 20.83, 20.86, 20.4, 15.2; IR (neat) ν cm^{-1}: 1669; $[\alpha]^{20}_D$ = +136 (c = 0.0318, MeOH); LRMS (FAB+) m/z: 577, 555; HRMS calcd for $C_{26}H_{38}N_2O_5S_3$ [M + Na]$^+$ 577.1841, found 577.1825.

(2*S*,3*Z*,5*S*,6*E*,8*R*)-2-(Phenylmethyl)-5-isopropyl-8-amino-9-mercapto-2,6-nonadienyl methionine, B956 (22). A 1 M solution of trimethylphosphine (0.12 mL, 0.12 mmol) was added to a solution of 29 mg **21** (0.0434 mmol) in 0.4 mL of 20:1:1 THF:H_2O:trifluoroacetic acid at room temperature. The solution was stirred at room temperature for 1 h and then concentrated under reduced pressure and purified by reverse phase HPLC. After evaporation of the HPLC eluent under vacuum, the residue was dissolved in 10:1 H_2O:acetonitrile and then lyophilized to afford 25 mg **22** (100%) as a white powder. ^{1}H NMR (CD_3OD) δ: 8.09 d (J = 8.2 Hz), 7.22−7.29 m, 7.16−7.20 m, 5.80 dd (J = 15.6, 7.8 Hz), 5.65 t (J = 10.5 Hz), 5.43 t (J = 10.5 Hz), 5.35−5.39 m, 4.44−4.48 m, 3.88−3.94 m, 3.81 q (J = 6.4 Hz), 3.59 td (J = 9.6, 6.4 Hz), 2.94−3.00 m, 2.80 dd (J = 14.2, 6.0 Hz), 2.70−2.75 m, 2.01−2.16 m, 2.01 s, 1.92−2.00 m, 1.70−1.77 m, 1.66 oct (J = 6.9 Hz), 0.94 d (J = 6.9 Hz), 0.91 d (J = 6.4 Hz); ^{13}C NMR (CD_3OD) δ: 175.9, 174.8, 141.13, 141.09, 140.4, 133.2, 130.4, 129.6, 129.7, 127.8, 125.2, 56.4, 52.4, 41.0, 33.6, 32.3, 31.0, 28.4, 20.8, 20.5, 15.2; IR (neat) ν cm^{-1}: 1670, 1636; $[\alpha]^{20}_D$ = +96.8 (c = 0.00935, MeOH); LRMS (FAB+) m/z: 487, 465; HRMS calcd for $C_{24}H_{36}N_2O_3S_2$ [M + Na]$^+$ 487.2065, found 487.2083.

Methyl (2*R*,3*E*,5*S*,6*E*)-2-(Phenylmethyl)-5-isopropyl-7-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2,6-heptadienyl Methionine (24). Compound **24** (64 mg) was obtained from 65 mg of **15** (0.137 mmol) using the procedure described above for the preparation of **18** from **12**. After additional purification by reverse phase HPLC, 58 mg pure of **24** was obtained (68%). ^{1}H NMR (CD_3OD) δ: 8.30 d (J = 7.8 Hz), 7.22−7.26 m, 7.13−7.17 m, 5.43−5.56 m, 4.79 br m, 4.49−4.53 m, 3.64 s, 3.27−3.32 m, 2.90−2.94 m, 3.05 dd (J = 7.8, 13.7 Hz), 2.73 dd (J = 7.3, 13.7 Hz), 2.56 d (J = 11.9), 2.34−2.49 m, 2.02−2.10 m, 2.04 s, 1.81−1.93 m, 1.76−1.77 m, 1.54 oct (J = 6.9), 1.46 s, 0.86 d (J = 6.9 Hz), 0.83 d (J = 6.4 Hz); ^{13}C NMR (CD_3OD) δ: 176.5, 173.7, 154.1, 140.6, 136.2, 134.6, 130.43, 130.29, 129.46, 129.36, 129.39, 127.31, 66.9, 54.02, 53.96, 53.5, 52.9, 52.83, 52.75, 52.62, 52.52, 39.7, 34.3, 33.8, 32.0, 31.2, 30.9, 29.0, 28.9, 20.9, 20.6, 15.4; IR (neat) ν cm^{-1}: 1745, 1691, 1647; $[\alpha]^{20}_D$ = −62.8 (c = 0.0532, $CHCl_3$); LRMS (FAB+) m/z: 641, 519; HRMS calcd for $C_{33}H_{50}N_2O_5S_2$ [M + Na]$^+$ 641.3059, found 641.3041.

(2*R*,3*E*,5*S*,6*E*)-2-(Phenylmethyl)-5-isopropyl-7-[(5*R*)-*N*-[(*tert*-butyloxy)carbonyl]-2,2-dimethyl-4-thiazolidinyl]-2,6-heptadienyl Methionine (25). Acid **25** (49 mg, 86%) was obtained from 58 mg of **24** (0.094 mmol) using the procedure described above for the preparation of **19**. ^{1}H NMR (CD_3OD) δ: 7.21−7.24 m, 7.13−7.18 m, 5.44−5.49 m, 4.77 br m, 4.51 dd (J = 4.6, 9.6 Hz), 3.27−3.31 m, 3.06 dd (J = 13.7, 6.9 Hz), 2.74 dd (J = 7.8, 13.7 Hz), 2.55 d (J = 11.9), 2.37−2.51 m, 2.05−2.14 m, 2.05 s, 1.88−1.95 m, 1.76 m, 1.55 oct (J = 6.9 Hz), 1.45 s, 0.77−0.85 m; ^{13}C NMR (CD_3OD) δ: 176.5, 175.0, 154.1, 140.7, 136.3, 134.5, 130.4, 129.5, 129.3, 127.3, 81.4, 66.9, 53.97, 53.92, 53.50, 52.5, 52.3, 39.6, 34.3, 33.8, 32.4, 31.3, 29.0, 28.9, 20.9, 20.6, 15.4; IR (neat) ν cm^{-1}: 1735, 1691; $[\alpha]^{20}_D$ = −64.7 (c = 0.0455, $CHCl_3$); LRMS (FAB+) m/z: 627, 505, 470; HRMS calcd for $C_{32}H_{48}N_2O_5S_2$ [M + Na]$^+$ 627.2902, found 627.2885.

(2*R*,3*E*,5*S*,6*E*,8*R*)-2-Phenylmethyl-5-isopropyl-8-[(*N*-*tert*-butyloxy)carbonylamino]-9-(carbomethoxysulfenylthio)-2,6-nonadienyl Methionine (26). Compound **26** (49 mg, 92%) was obtained from 48 mg of **25** (0.080 mmol) using the procedure described above for the preparation of **20**. ^{1}H NMR (CD_3OD) δ: 7.22−7.25 m, 7.13−7.18 m, 5.53 ddd (J = 15.1, 7.3, 0.9 Hz), 5.45 dd (J = 15.1, 8.2 Hz), 5.38 dd (J = 15.6, 7.8 Hz), 5.15 ddd (J = 15.6, 6.4, 0.9 Hz), 4.77 br m, 4.52 dd (J = 4.6, 9.6 Hz, 4.21 br q, (J = 6.4 Hz), 3.90 s, 3.27−3.32 m, 3.06 dd (J = 13.7, 6.9 Hz), 2.83−2.91 m, 2.75 dd (J = 13.7, 8.7 Hz), 2.47−2.53 m, 2.39−2.44 m, 2.55 d (J = 11.9 Hz), 2.10−2.12 m, 2.05 s, 1.90−1.95 m, 1.57 oct (J = 6.4), 0.81 d (J = 1.4 Hz), 0.79 d (J = 0.9 Hz); ^{13}C NMR (CD_3OD) δ: 176.6, 175.1, 171.4, 157.6, 140.7, 135.7, 135.3, 130.8, 130.4, 129.5, 129.4, 127.3, 80.4, 56.4, 56.3, 56.2, 53.74, 53.68, 53.50, 53.10, 52.5, 52.3, 45.4, 39.5, 33.6, 32.4, 31.3, 31.0, 29.0, 28.9, 20.6, 20.5, 15.4; IR (neat) ν cm^{-1}: 1735, 1649; $[\alpha]^{20}_D$ = −9.1 (c = 0.0427, $CHCl_3$); LRMS (FAB+) m/z: 677, 599, 555; HRMS calcd for $C_{31}H_{46}N_2O_7S_3$ [M + Na]$^+$ 677.2365, found 677.2369.

(2*R*,3*E*,5*S*,6*E*,8*R*)-2-(Phenylmethyl)-5-isopropyl-8-amino-9-(carbomethoxysulfenylthio)-2,6-nonadienyl Methionine (27). Compound **27** (36 mg, 72%) was obtained from 49 mg of **26** (0.075 mmol) using the procedure described above for the preparation of **21**. ^{1}H NMR (CD_3OD) δ: 7.20−7.25 m, 7.14−7.18 m, 5.88 dd (J = 15.6, 8.2 Hz), 5.43−5.53 m, 5.34 ddd (J = 15.6, 8.2, 0.9 Hz), 4.50 dd (J = 4.6, 9.6 Hz), 3.90−3.96 m, 3.94 s, 3.30−3.35 m, 3.02−3.11 m, 2.76 dd (J = 13.7, 8.2 Hz), 2.46−2.55 m, 2.37−2.43 m, 2.05−2.15 m, 2.05 s, 1.88−1.94 m, 1.63 oct (J = 6.4), 0.83 d (J = 5.0 Hz), 0.83 d (J = 4.6 Hz); ^{13}C NMR (CD_3OD) δ: 176.5, 175.0, 171.8, 141.5, 141.4, 140.6, 134.6, 131.5, 130.4, 130.3, 129.5, 129.4, 127.5, 127.3, 125.4, 57.0, 56.9, 56.7, 54.0, 53.9, 53.5, 53.3, 52.5, 43.3, 43.2, 39.5, 33.5, 33.4, 32.3, 31.3, 20.6, 20.4, 15.3; IR (neat) ν cm^{-1}: 1718, 1668; $[\alpha]^{20}_D$ = +20.0 (c = 0.0364, $CHCl_3$); LRMS (FAB+) m/z: 577, 555, 159; HRMS calcd for $C_{26}H_{38}N_2O_5S_3$ [M + Na]$^+$ 577.1841, found 577.1844.

(2*R*,3*E*,5*S*,6*E*,8*R*)-2-(Phenylmethyl)-5-isopropyl-8-amino-9-mercapto-2,6-nonadienyl Methionine, B957 (23). B957 (**23**, 30 mg, 96%) was obtained from 36 mg of **27** (0.0539 mmol) using the procedure described above for the preparation of **22**.

^{1}H NMR (CD_3OD) δ: 8.26 d (J = 8.2 Hz), 7.20−7.26 m, 7.14−7.19 m, 5.82 dd (J = 15.6, 8.2 Hz), 5.44−5.54 m, 5.33 ddd (J = 15.6, 7.8, 0.9 Hz), 4.48−4.52 m, 3.82 q (J = 6.4 Hz), 3.29−3.35 m, 3.07 dd (J = 13.7, 6.9 Hz), 2.71−2.83 m, 2.37−2.43 m, 2.06−2.15 m, 2.06 s, 1.88−2.04 m, 1.63 oct (J = 6.9 Hz), 0.84 d (J = 4.1 Hz), 0.83 d (J = 4.1 Hz); ^{13}C NMR (CD_3OD) δ: 176.5, 175.0, 141.0, 140.9, 140.6, 134.8, 131.4, 130.4, 130.3, 129.5, 127.5, 126.0, 125.9, 56.6, 56.5, 54.0, 53.9, 53.3, 52.5, 39.5, 33.4, 32.2, 31.3, 28.5, 28.4, 28.3, 20.6, 20.4, 17.3, 15.3; $[\alpha]^{20}_D = -41.4$ (c = 0.00959, CH_3OH); LRMS (FAB+) m/z: 487; HRMS calcd for $C_{24}H_{36}N_2O_3S_2$ $[M + Na]^+$ 487.2065 found 487.2059.

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Supporting Information Available: ^{1}H NMR for compounds **1**−**3** and **5**−**27** and ^{13}C NMR spectra for compounds **1**, **2a**, **2b**, **3**, **5**−**7**, and **9**−**27**; complete X-ray data for **7a** and **12** (89 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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