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Aminooxylation Horner–Wadsworth–Emmons Sequence for the Synthesis of Enantioenriched γ-Functionalized Vinyl Sulfones

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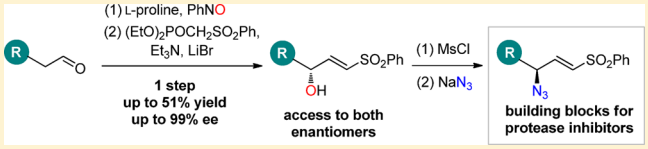
Supporting Information

ABSTRACT: An operationally simple protocol for the synthesis of γ-hydroxy vinyl sulfones has been developed using a proline-based aldehyde aminooxylation, followed by a vinyl sulfone forming Horner–Wadsworth–Emmons olefination. The adducts, formed in high enantiopurity, were subsequently converted to γ-azido vinyl sulfones, and azide–alkyne click chemistry enabled the synthesis of vinyl sulfone-based triazoles as potential nonpeptidic cysteine protease inhibitors.



INTRODUCTION

Vinyl sulfones are useful functionalized building blocks that have frequently been used in the assembly of target molecules.[1,2] Additionally, since the mid-1990s certain members of this wider family are recognized to be potent enzyme inhibitors (see Figure 1 for representative vinyl sulfone

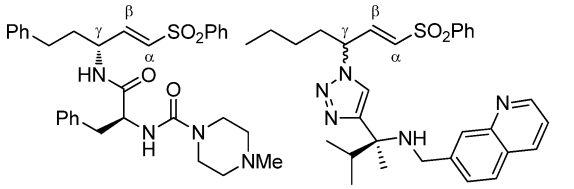
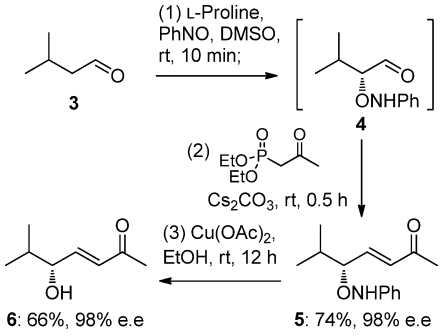


Figure 1. Representative vinyl sulfone-based enzyme inhibitors.

cysteine protease inhibitors).[3] In relation to the latter, we became interested in developing a means to access chiral γ-functionalized vinyl sulfones in order to prepare targets not directly available from chiral pool amino acid-based starting materials, so that ultimately we can study their antiparasitic behavior.[4] This type of compound has been prepared in racemic and enantioenriched/pure form via sequences involving several steps. As a rule, these routes are focused on a single target and, therefore, do not readily provide access to the enantiomeric series or readily incorporate alternative structural characteristics.[5]

In 2003, Zhong, MacMillan, and Hayashi independently[6] published their findings concerning the enamine-based[7] asymmetric α-aminooxylation of a range of aldehydes using proline and nitrosobenzene (as an electrophilic oxygen source), in order to form α-aniloxy aldehydes of the type **4**. These aldehydes, bearing an electronegative group in the α-position, are complex in terms of structure. However, the material from the crude reaction mixture participated in typical aldehyde chemistry (borohydride-based reduction, reductive amination, etc.). In terms of stereochemistry, for aliphatic aldehydes, L-proline afforded the *R*-enantiomeric series.[8] Shortly after these initial reports, Zhong demonstrated that the aminooxylation could be telescoped in one-pot with a Horner–Wadsworth–Emmons (HWE) olefination, generating γ-aniloxy-α,β-unsaturated ketones (e.g., **5**) in good overall yield and excellent enantioselectivity (Scheme 1).[9] During these processes it was

Scheme 1. Zhong's Aminooxylation HWE Reaction Sequence



reported that the weak N–O bond was conserved and that the products could be reduced either by hydrogenolysis or copper-mediated conditions providing the corresponding enantioenriched secondary alcohols (e.g., **6**). Since the original report, this sequence has been utilized by several groups for the preparation of carbonyl compounds bearing γ-stereogenic centers.[10] However, to date, this process has not been transferred to sulfones. Described here is a simple protocol to access enantioenriched γ-hydroxy and γ-amino vinyl sulfones.

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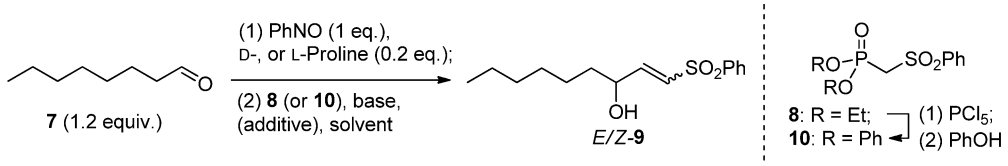
Table 1. Aminooxylation Vinyl Sulfone Forming HWE Reaction for the Preparation of 9



Entry	Conditions	Product	Yield[a]	e.e.[b]
1	(1) L-Proline, DMSO (0.2 M), rt, 20 min; (2) **8** (2 eq.), Cs_2CO_3 (1.4 eq.), rt, 24 h	(*R*,*E*)-**9**	11%	96%
2	(1) L-Proline, DMSO (0.2 M), rt, 30 min; (2) **8** (2 eq.), DBU, LiCl, MeCN, rt, 24 h	(*R*,*E*)-**9**	18%	97%
3	(1) D-Proline, $CHCl_3$ (0.2 M), 0 °C, 2.5 h; (2) **8** (2 eq.), Et_3N, LiBr, MeCN, rt, 24 h	(*S*,*E*)-**9**	32%	97%
4	(1) L-Proline, MeCN (0.2 M), 0 °C, 2 h; (2) **8** (2 eq.), Et_3N, LiBr, MeCN, rt, 24 h	(*R*,*E*)-**9**	45-51%[c]	97%
5	(1) L-Proline, MeCN (0.2 M), 0 °C, 2 h; (2) **8** (2 eq.), NaH, THF, 0 °C to rt, 24 h	(*R*,*E*)-**9**	42%	98%
6	(1) L-/D-Proline, MeCN (0.2 M), 0 °C, 2 h; (2) **10** (2 eq.), NaI, DBU, THF, −78 °C to rt, 24 h	(*R*,*Z*)-**9**	9%[d]	98%
		(*S*,*Z*)-**9**	10%[e]	97%

[a]Yields following purification by flash column chromatography. [b]Enantiomeric excess determined by chiral HLPC analysis. [c]Optimum yield obtained when **7** was distilled prior to reaction. [d]*E*-**9** (19%) also isolated. [e]*E*-**9** (17%) also isolated.

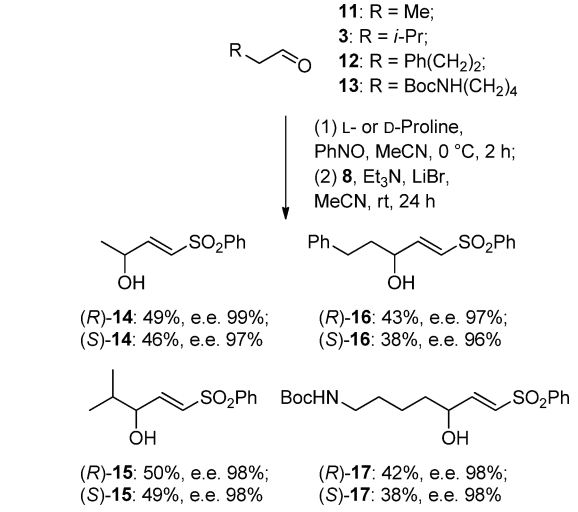
RESULTS AND DISCUSSION

For the initial study, octanal **7** was selected for optimization. As shown in Table 1, use of Zhong's one-pot reaction conditions in the presence of sulfonyl phosphonate **8** gave the *trans*-γ-hydroxy vinyl sulfone **9** in only very low yield (entry 1). None of the anticipated aniloxy adduct (of the type **5**, Scheme 1) was detected, and when the reaction period for the HWE phase was reduced, negligible amounts of sulfone-based material were produced.[11] Although the yield was disappointing, the enantiomeric excess of the adduct *E*-**9** proved high and was consistent with literature reports for this type of reaction.[6,9,10] As entry 2 indicates, only a slight improvement in chemical yield was observed when Masamune–Roush[12,10d] (or Rathke's[13] $MgBr_2$-based conditions; not shown) for the HWE reaction were employed. We then opted to change the solvent for the aminooxylation, moving to MacMillan's $CHCl_3$[6b] and Hayashi's MeCN[6c] at 0 °C rather than room temperature. In both instances this change in reaction medium and temperature resulted in a slower initial reaction (i.e., 2–2.5 h), and better overall yields were obtained, particularly using Rathke's mild HWE conditions,[13] which were optimized to 51% when **7** was distilled prior to the reaction (entries 3 and 4). In relation to the chemical yield we were concerned that some material remained at the aniloxy intermediate, therefore the reported copper-mediated process for N–O bond heterolysis ($CuSO_4 \cdot 5H_2O$ in MeOH)[6] was performed on the crude reaction mixture following HWE olefination. This did not result in any increase in yield. A traditional sodium hydride-based HWE reaction gave *E*-**9** in 42% yield (entry 5).[5h] We also attempted a *Z*-selective Ando HWE olefination[14] using phosphonate **10** and literature conditions deviating slightly from our optimal procedure (entry 6). However, in this instance only moderate yields and poor *Z*-selectivity were observed. Nonetheless, the separation of the geometric isomers by column chromatography was facile, and optically active *Z*-**9** was fully characterized.

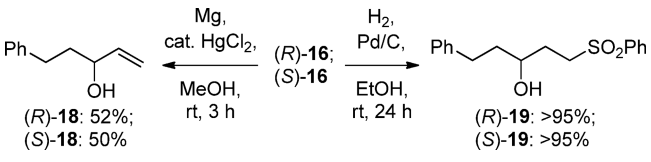
We then applied our optimized reaction conditions, with L- and D-proline, to a small range of aldehydes (Scheme 2). Using propanal **11** and the optimum conditions identified from the study included in Table 1, both enantiomers of **14** were isolated in moderate yields and excellent enantioselectivities.

Use of the branched aldehyde **3** similarly provided (*R*)- and (*S*)-**15**. 4-Phenylbutanal **12** and the ω-amino-functionalized aldehyde **13** gave (*R*)- and (*S*)-**16** and **17** in slightly poorer yields than their alkyl counterparts, but pleasingly the enantiomeric excess of the adducts was comparable. In order to demonstrate the utility of the γ-hydroxy-α,β-unsaturated sulfones, further conversions of the initial adducts were considered. As shown in Scheme 3, (*R*)- and (*S*)-**16** engage in selective reductions. Magnesium(0) in the presence of catalytic amounts of Hg(II) led to a reductive cleavage of the C–S bond to form (*R*)- and (*S*)-**18** in moderate yield.[15] Use of typical hydrogenation conditions in order to generate a remote stereocenter provided (*R*)- and (*S*)-**19** in essentially quantitative yield.[5c] In both instances no erosion of enantiopurity was detected.

Scheme 2. Substrate Scope for the Aminooxylation HWE Sequence



Scheme 3. Complementary Reductions of (*R*)- and (*S*)-16



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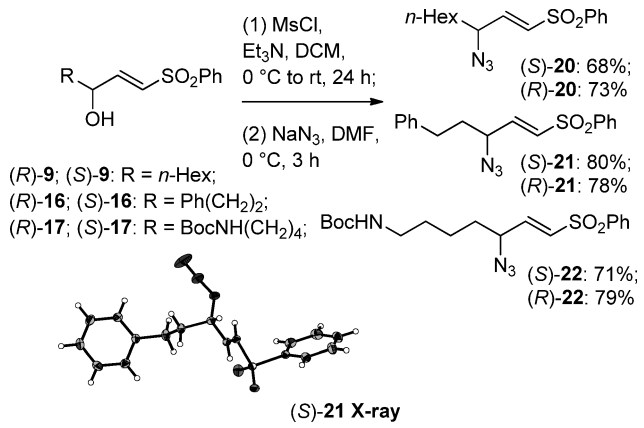
The stereocontrolled conversion of the allylic hydroxyl group into an azido group was considered next. Under direct Mitsunobu-type conditions,[16] none of the hoped for γ-azido vinyl sulfone was observed due to issues with vinylic to allylic sulfone isomerization[1f] and decomposition. However, as shown in Scheme 4, following a mesylation-based sequence,[17] both

Scheme 4. Synthesis of γ-Azido Vinyl Sulfones and Single Crystal X-ray Structure Image of (*S*)-21[a]



[a]Ortep plots to 50% probability.

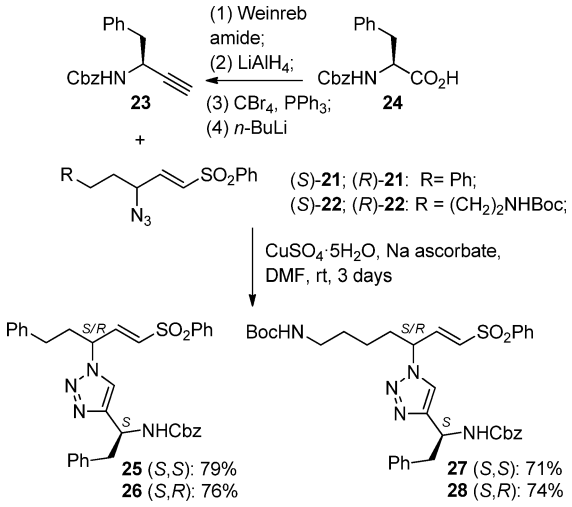
enantiomers of **9**, **16**, and **17** were converted with inversion into the corresponding azides **20**, **21**, and **22**. No issue with double-bond isomerization or the loss of optical purity was observed during the course of the reactions. In the case of (*S*)-**21**, single crystal X-ray diffraction supported the structural assignment.[18]

With the γ-azido vinyl sulfones in hand, their copper(I) catalyzed azide−alkyne click reaction (CuAAC)[19] with phenylalanine derived alkyne **23** (prepared from the corresponding aldehyde via a Corey−Fuchs alkynylation)[20] was considered. 1,4-Disubstituted-1,2,3-triazoles are recognized to be proteolytically stable motifs that effectively mimic peptide bonds; they are therefore of significant interest from a biological standpoint (for example, compound **2**, Figure 1).[21,22]

Both enantiomers of azide **21** were reacted with phenylalanine-based alkyne **23** using DMF as the solvent under otherwise standard conditions to provide triazoles **25** and **26** as single diastereoisomers (Scheme 5). These vinyl sulfone-containing homophenylalanine analogues can be considered to be nonpeptidic bioisosteres[21] of compounds of type **1**. Furthermore, triazoles **27** and **28**, similarly obtained from *R*- and *S*-**22**, can be viewed as Boc-protected lysine analogues. This methodology therefore alleviates the reliance on naturally occurring amino acid residues for incorporation into the γ-position of vinyl sulfone-based protease inhibitors.

In summary, we have developed a straightforward synthesis of γ-oxygen or nitrogen-substituted vinyl sulfones, whereby, the desired enantiomer can be accessed in good enantiomeric excess. The reaction conditions were conducted in an aerobic atmosphere without the need for dry solvents and, in contrast to previous reports,[9,10] avoid an additional N−O bond cleavage step. To highlight the utility of this reaction, we have shown that these compounds can easily be converted to the corresponding azides using mesylation/azide displacement chemistry and found application in the synthesis of diastereomeric triazoles, which are potential cysteine protease

Scheme 5. CuAAC Reaction for the Synthesis of 1,4-Disubstituted 1,2,3-Triazole-Based Vinyl Sulfone Peptidomimetics



inhibitor scaffolds. Chemoselective reduction of the azido group is currently under investigation in our laboratory in order to access γ-amino vinyl sulfones.

EXPERIMENTAL SECTION

General Directions. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 400 MHz system spectrometers, and coupling constants *J* are quoted in Hertz. ^{1}H and ^{13}C NMR chemical shift assignments are based on two-dimensional NMR experiments including ^{1}H−^{1}H gCOSY, DEPT, HSQC, and HMBC. High-resolution mass spectra were carried out on a mass spectrometer with a TOF analyzer. Infrared spectra were recorded on a FT-IR spectrometer. Optical rotation data are quoted in units of 10^{-1} deg cm^2 g^{-1}. Chiral phase HPLC was performed under the conditions provided, and enantiomeric excess was calculated on the basis of the average between the 210 and 230 nm wavelength traces. Reagents were obtained from commercial suppliers and were used without further purification. Dichloromethane was used as received except for the Corey−Fuchs dibromination reaction, where it was dried over activated 4 Å molecular sieves. Tetrahydrofuran was freshly distilled from sodium-benzophenone ketyl radical under nitrogen.

General Procedure for Aminooxylation Horner−Wadsworth−Emmons (AO-HWE) Reaction. Note: The AO-HWE reactions do not require anhydrous/inert conditions or dry solvents. At 0 °C, to a stirred solution of aldehyde (1.2 equiv) and nitrosobenzene (1.0 equiv) in MeCN (0.2 M based on aldehyde) was added proline (0.2 equiv), and the reaction mixture was stirred at 0 °C for 2 h after which time the reaction turned from clear turquoise green to opaque orange, indicating consumption of nitrosobenzene. Meanwhile, at room temperature in a separate flask, to a stirred solution of diethyl [(phenylsulfonyl)methyl]phosphonate **8** (2.0 equiv) and LiBr (2.0 equiv) in MeCN (0.5 M) was added Et_3N (2.0 equiv), and the reaction mixture was stirred for 10 min. Note: this reaction can be set up once the AO reaction has reached completion, i.e., turned orange. The contents of the AO flask were then transferred to the HWE flask using a Pasteur pipet. The AO flask was then rinsed with MeCN (1−4 mL depending on reaction scale), and the resulting clear orange solution was stirred for 24 h at room temperature. The reaction mixture was quenched with HCl (1 M, 10−20 mL depending on scale of the reaction) to give a dark clear burgundy solution, and the mixture was extracted with CH_2Cl_2 (20−40 mL depending on scale of the reaction). The layers were separated, and the aqueous layer was re-extracted with CH_2Cl_2 (10−20 mL) after which the aqueous layer was very pale yellow or colorless. The combined organic layers were washed with brine (10−20 mL), dried over $MgSO_4$, and filtered,

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and the solvent was removed in vacuo to give the crude product as a thick burgundy oil. Purification by column chromatography gave γ-hydroxy vinyl sulfones as orange/yellow solids or orange/yellow oils.

(*R*,*E*)-1-(Phenylsulfonyl)non-1-en-3-ol (*R*)-*E*-9.[5a,d] AO flask: Octanal **7** (0.22 mL, 1.41 mmol, 1.2 equiv), nitrosobenzene (129 mg, 1.20 mmol, 1.0 equiv), and L-proline (28 mg, 0.24 mmol, 0.2 equiv) in MeCN (6 mL) were stirred for 2 h at 0 °C. HWE flask: Diethyl [(phenylsulfonyl)methyl]phosphonate **8** (701 mg, 2.40 mmol, 2.0 equiv), LiBr (230 mg, 2.65 mmol, 2.2 equiv), and Et_3N (0.33 mL, 2.37 mmol, 2.0 equiv) in MeCN (5 mL + 1 mL rinse). After aqueous workup, purification by column chromatography (*c*-Hex/EtOAc; 6:1) gave γ-hydroxy vinyl sulfone (*R*)-**9** as a pale yellow solid (161 mg, 47%). Mp 58−62 °C; Lit.[5c] 64−65 °C. R_f = 0.5 (*c*-Hex/EtOAc; 1:1). IR (film) ν_{max} = 3062, 2927, 2858, 1628, 1446, 1306, 1180, 1146, 1086, 968 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3H, CH_3), 1.20−1.46 (m, 8H, CH_2), 1.50−1.62 (m, 2H, CH_2), 1.81 (s (br), 1H, OH), 4.35−4.42 (m, 1H, CH), 6.60 (dd, *J* = 15.0, 2.0 Hz, 1H, CH), 6.99 (dd, *J* = 15.0, 4.0 Hz, 1H, CH), 7.54 (t, *J* = 7.5 Hz, 2H, ArH), 7.62 (t, *J* = 7.5 Hz, 1H, ArH), 7.89 (d, *J* = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5 (CH_2), 25.1 (CH_2), 29.0 (CH_2), 31.6 (CH_2), 36.4 (CH_2), 70.4 (CH), 127.6 (CH), 129.3 (CH), 129.6 (CH), 133.4 (CH), 140.3 (C), 148.1 (CH) ppm. $[\alpha]_D$ = −31 (*c* = 1.0, $CHCl_3$). HPLC analysis (Chiralcel OJ-H column) heptane/ethanol; 95:5 (1.0 mL/min): t_r minor (*S*)-**9** = 22.9 min, t_r major (*R*)-**9** = 24.5 min; 97% ee.

(*S*,*E*)-1-(Phenylsulfonyl)non-1-en-3-ol (*S*)-*E*-9.[5a,d] AO flask: Octanal **7** (0.22 mL, 1.41 mmol, 1.2 equiv), nitrosobenzene (125 mg, 1.17 mmol, 1.0 equiv), and D-proline (29 mg, 0.25 mmol, 0.2 equiv) in MeCN (6 mL) were stirred for 2 h at 0 °C. HWE flask: Diethyl [(phenylsulfonyl)methyl]phosphonate **8** (694 mg, 2.37 mmol, 2.0 equiv), LiBr (212 mg, 2.44 mmol, 2.1 equiv), and Et_3N (0.33 mL, 2.37 mmol, 2.0 equiv) in MeCN (5 mL + 1 mL rinse). After aqueous workup, purification by column chromatography (*c*-Hex/EtOAc; 6:1) gave γ-hydroxy vinyl sulfone (*S*)-**9** as a pale yellow solid (169 mg, 51%). $[\alpha]_D$ = +39 (*c* = 1.0, $CHCl_3$); Lit.[5c] $[\alpha]_D$ = +44.4 (*c* = 1.0, $CHCl_3$). HPLC analysis (Chiralcel OJ-H column) heptane/ethanol; 95:5 (1.0 mL/min): t_r major (*S*)-**9** = 23.5 min, t_r minor (*R*)-**9** = 25.4 min; 97% ee.

Diphenyl [(phenylsulfonyl)methyl]phosphonate 10. Diethyl [(phenylsulfonyl)methyl]phosphonate **8** (502 mg, 1.71 mmol, 1.0 equiv) was melted in a 5 mL round-bottom flask with a heat gun. To this was added PCl_5 (913 mg, 4.38 mmol, 2.6 equiv), and the reaction mixture was heated at 85 °C for 18 h. Vacuum distillation (120 °C; ca. 1 mmHg) to remove $POCl_3$ and PCl_5 gave the residual crude dichloride as a black tar which was dissolved in toluene (1 mL) and cooled to 0 °C. A toluene solution (1 mL) of phenol (323 mg, 3.43 mmol, 2.0 equiv) and Et_3N (0.60 mL, 4.25 mmol, 2.5 equiv) was then added to the above solution. The reaction mixture stirred for 1.5 h at room temperature, and the resulting brown mixture was diluted with EtOAc (10 mL). The solution was filtered and washed with EtOAc (5 mL). The filtrate was washed with 1 M NaOH (3 × 10 mL), sat. aq. NH_4Cl (10 mL), brine (10 mL), dried over $MgSO_4$, and filtered. Solvent was removed in vacuo to give a crude brown oil. Purification by column chromatography (*c*-Hex/EtOAc; 3:1) gave phosphonate **10** as a white powdery solid (257 mg, 39%). Mp 69−72 °C. R_f = 0.1 (*c*-Hex/EtOAc; 3:1). IR (film): ν_{max} 1590, 1490, 1448, 1326, 1282, 1213, 1185, 1160, 1110, 1086, 1025, 952 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.05 (d, J_{PH} = 17.0 Hz, 2H, CH_2), 7.14 (d, *J* = 7.5 Hz, 4H, ArH), 7.19 (t, *J* = 7.5 Hz, 2H, ArH), 7.31 (t, *J* = 7.5 Hz, 4H, ArH), 7.57 (t, *J* = 7.5 Hz, 2H, ArH), 7.67 (t, *J* = 7.5 Hz, 1H, ArH), 8.04 (d, *J* = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.3 (d, J_{PC} = 141.5 Hz, CH_2), 120.6 (d, J_{PC} = 4.5 Hz, CH), 125.8 (d, J_{PC} = 1.5 Hz, CH), 128.5 (CH), 129.3 (CH), 129.9 (d, J_{PC} = 1.0 Hz, CH), 134.4 (CH), 139.8 (C), 149.6 (d, J_{PC} = 8.5 Hz, C) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 3.9 ppm. HRMS (ES^+): $C_{19}H_{17}O_5PNaS$ (MNa^+) calcd 411.0432; found 411.0446. Anal. calcd $C_{19}H_{17}O_5PS$: C, 58.76; H, 4.41; found C, 58.61; H. 4.26.

(*R*,*Z*)-1-(Phenylsulfonyl)non-1-en-3-ol (*R*)-*Z*-9. AO flask: Octanal **7** (65 μL, 0.42 mmol, 1.2 equiv), nitrosobenzene (38 mg, 0.35 mmol, 1.0 equiv), and L-proline (8 mg, 0.07 mmol, 0.2 equiv) in MeCN (2 mL) were stirred for 2 h at 0 °C. HWE flask: At −78 °C, diphenyl [(phenylsulfonyl)methyl]phosphonate **10** (269 mg, 0.69 mmol, 2.0 equiv), NaI (105 mg, 0.70 mmol, 2.0 equiv), and DBU (0.11 mL, 0.74 mmol, 2.1 equiv) were stirred in THF (4 mL). The contents of the AO flask were transferred (0.5 mL MeCN rinse), and the reaction mixture stirred overnight warming slowly to room temperature. After 24 h, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, and filtered, and solvent was removed in vacuo to give the crude product. Purification by column chromatography (*c*-Hex/EtOAc; 6:1) gave (*R*)-*E*-**9** (19 mg, 19%); R_f = 0.5 (*c*-Hex/EtOAc; 1:1). Further elution gave (*R*)- *Z*-**9** as a yellow oil (9 mg, 9%). R_f = 0.4 (*c*-Hex/EtOAc; 1:1). IR (film): ν_{max} 2927, 2858, 1626, 1446, 1375, 1306, 1147, 1084 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.0 Hz, 3H, CH_3), 1.20−1.48 (m, 8H, CH_2), 1.49−1.70 (m, 2H, CH_2), 2.47 (s (br), 1H, OH), 5.20 (app. q, *J* = 7.0 Hz, 1H, CH), 6.24 (dd, *J* = 11.5, 8.0 Hz, 1H, CH), 6.30 (d, *J* = 11.5 Hz, 1H, CH), 7.57 (t, *J* = 7.5 Hz, 2H, ArH), 7.65 (t, *J* = 7.5 Hz, 1H, ArH), 7.93 (d, *J* = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6 (CH_2), 25.0 (CH_2), 29.1 (CH_2), 31.7 (CH_2), 36.6 (CH_2), 66.4 (CH), 127.4 (CH), 129.4 (CH), 130.4 (CH), 133.7 (CH), 140.9 (C), 148.1 (CH) ppm. HRMS (EI^+): $C_{15}H_{22}O_3S$ (M^+) calcd 282.1290; found 282.1283. $[\alpha]_D$ = −4 (*c* = 0.3, $CHCl_3$). HPLC analysis (Chiralcel OJ-H column) heptane/ethanol; 95:5 (1.0 mL/min): t_r major (*R*)-*Z*-**9** = 24.9 min, t_r minor (*S*)-*Z*-**9** = 26.6 min; 98% ee.

(*S*,*Z*)-1-(Phenylsulfonyl)non-1-en-3-ol (*S*)-*Z*-9. AO flask: Octanal **7** (18 μL, 0.12 mmol, 1.2 equiv), nitrosobenzene (11 mg, 0.10 mmol, 1.0 equiv), and D-proline (2 mg, 0.02 mmol, 0.2 equiv) in MeCN (0.5 mL) were stirred for 2 h at 0 °C. HWE flask: At −78 °C, diphenyl [(phenylsulfonyl)methyl]phosphonate **10** (70 mg, 0.18 mmol, 1.8 equiv), NaI (31 mg, 0.21 mmol, 2.0 equiv), and DBU (27 μL, 0.18 mmol, 1.8 equiv) were stirred in THF (2 mL). The contents of the AO flask were transferred (0.5 mL MeCN rinse). After aqueous workup as above, purification by column chromatography (*c*-Hex/EtOAc; 6:1) gave (*S*)-*E*-**9** (5 mg, 17%); R_f = 0.5 (*c*-Hex/EtOAc; 1:1). Further elution gave (*S*)-*Z*-**9** as a yellow oil (3 mg, 10%). R_f = 0.4 (*c*-Hex/EtOAc; 1:1). $[\alpha]_D$ = +3 (*c* = 0.3, $CHCl_3$). HPLC analysis (Chiralcel OJ-H column) heptane/ethanol; 95:5 (1.0 mL/min): t_r minor (*R*)-*Z*-**9** = 25.3 min, t_r major (*S*)-*Z*-**9** = 26.3 min; 97% ee.

(*R*,*E*)-4-(Phenylsulfonyl)but-3-en-2-ol (*R*)-14.[5a,d] AO flask: Propanal **11** (0.10 mL, 1.39 mmol, 1.2 equiv), nitrosobenzene (128 mg, 1.20 mmol, 1 equiv), and L-proline (28 mg, 0.24 mmol, 0.2 equiv) were stirred in MeCN (6 mL) for 2 h at 0 °C. HWE flask: Diethyl [(phenylsulfonyl)methyl]phosphonate **8** (683 mg, 2.34 mmol, 2.0 equiv), LiBr (207 mg, 2.38 mmol, 2.0 equiv), and Et_3N (0.33 mL, 2.37 mmol, 2.0 equiv) in MeCN (5 mL + 1 mL rinse). After aqueous workup, purification by column chromatography (*c*-Hex/EtOAc; 1:1) gave γ-hydroxy vinyl sulfone (*R*)-**14** as an orange solid (124 mg, 49%). Mp = 79−83 °C; Lit.[5c] 94−95 °C. R_f = 0.2 (*c*-Hex/EtOAc; 1:1). IR (film): ν_{max} = 3487, 3064, 2981, 1626, 1586, 1450, 1282, 1197, 1141, 1083, 1037, 985 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.5 Hz, 3H, CH_3), 1.90 (s (br), 1H, OH), 4.55 (qdd, *J* = 6.5, 3.5, 2.0 Hz, 1H, CH), 6.60 (dd, *J* = 15.0, 2.0 Hz, 1H, CH), 6.99 (dd, *J* = 15.0, 3.5 Hz, 1H, CH), 7.54 (t, *J* = 7.5 Hz, 2H, ArH), 7.63 (t, *J* = 7.5 Hz, 1H, ArH), 7.89 (d, *J* = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.5 (CH_3), 66.5 (CH), 127.7 (CH), 129.28 (CH), 129.29 (CH), 133.4 (CH), 140.2 (C), 148.7 (CH) ppm. $[\alpha]_D$ = −34 (*c* = 1.0, $CHCl_3$). HPLC analysis (Chiralcel OJ-H column) heptane/ethanol; 90:10 (1.0 mL/min): t_r minor (*S*)-**14** = 24.4 min, t_r major (*R*)-**14** = 25.9 min; 99% ee.

(*S*,*E*)-4-(Phenylsulfonyl)but-3-en-2-ol (*S*)-14.[5a,d] AO flask: Propanal **11** (0.10 mL, 1.39 mmol, 1.2 equiv), nitrosobenzene (127 mg, 1.19 mmol, 1.0 equiv), and D-proline (27 mg, 0.23 mmol, 0.2 equiv) in MeCN (6 mL) were stirred for 2 h at 0 °C. HWE flask: Diethyl [(phenylsulfonyl)methyl]phosphonate **8** (685 mg, 2.34 mmol, 2.0 equiv), LiBr (210 mg, 2.42 mmol, 2.0 equiv), and Et_3N (0.33 mL, 2.37 mmol, 2.0 equiv) in MeCN (5 mL + 1 mL rinse). After aqueous workup, purification by column chromatography (*c*-Hex/EtOAc; 1:1) gave γ-hydroxy vinyl sulfone (*S*)-**14** as an orange solid (115 mg, 46%).

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$[\alpha]_D$ = +32 (c = 1.0, $CHCl_3$); Lit.[5c] $[\alpha]_D$ = +42.9 (c = 1.0, $CHCl_3$). HPLC analysis (Chiralcel OJ-H column) heptane/ethanol; 90:10 (1.0 mL/min): t_r major (*S*)-**14** = 24.4 min, t_r minor (*R*)-**14** = 26.0 min; 97% ee.

(*R*,*E*)-4-Methyl-1-(phenylsulfonyl)pent-1-en-3-ol (*R*)-15.[5a,d] AO flask: Isovaleraldehyde **3** (156 mg, 1.81 mmol, 1.2 equiv), nitrosobenzene (162 mg, 1.51 mmol, 1.0 equiv), and L-proline (36 mg, 0.31 mmol, 0.2 equiv) in MeCN (9 mL) were stirred for 2 h at 0 °C. HWE flask: Diethyl [(phenylsulfonyl)methyl]phosphonate **8** (883 mg, 3.02 mmol, 2.0 equiv), LiBr (265 mg, 3.05 mmol, 2.0 equiv), and Et_3N (0.42 mL, 3.01 mmol, 2.0 equiv) in MeCN (7 mL + 2 mL) rinse. After aqueous workup, purification by column chromatography (CH_2Cl_2/EtOAc; 9:1) gave γ-hydroxy vinyl sulfone (*R*)-**15** as an orange solid (183 mg, 50%). Mp 55−59 °C; Lit.[5c] 60−62 °C. R_f = 0.4 (CH_2Cl_2/EtOAc; 9:1). IR (film): ν_{max} 3508, 3063, 2964, 2874, 1628, 1447, 1306, 1144, 1086, 1029, 972 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.91 (d, J = 7.0 Hz, 3H, CH_3), 0.95 (d, J = 7.0 Hz, 3H, CH_3), 1.82−1.95 (m, 2H, CH + OH), 4.18−4.23 (m, 1H, CH), 6.62 (d, J = 15.0 Hz, 1H, CH), 7.00 (dd, J = 15.0, 4.0 Hz, 1H, CH), 7.54 (t, J = 7.5 Hz, 2H, ArH), 7.62 (t, J = 7.5 Hz, 1H, ArH), 7.89 (d, J = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.2 (CH_3), 18.3 (CH_3), 33.7 (CH), 74.9 (CH), 127.6 (CH), 129.3 (CH), 130.6 (CH), 133.4 (CH), 140.4 (C), 146.9 (CH) ppm. $[\alpha]_D$ = −50 (c = 1.0, $CHCl_3$). HPLC analysis (Chiralcel OJ-H column) heptane/ethanol; 90:10 (1.0 mL/min): t_r minor (*S*)-**15** = 17.3 min, t_r major (*R*)-**15** = 18.3 min; 98% ee.

(*S*,*E*)-4-Methyl-1-(phenylsulfonyl)pent-1-en-3-ol (*S*)-15.[5a,d] AO flask: Isovaleraldehyde **3** (155 mg, 1.80 mmol, 1.2 equiv), nitrosobenzene (161 mg, 1.50 mmol, 1.0 equiv), and D-proline (36 mg, 0.31 mmol, 0.2 equiv) in MeCN (9 mL) were stirred for 2 h at 0 °C. HWE flask: Diethyl [(phenylsulfonyl)methyl]phosphonate **8** (886 mg, 3.03 mmol, 2.0 equiv), LiBr (261 mg, 3.01 mmol, 2.0 equiv), and Et_3N (0.42 mL, 3.01 mmol, 2.0 equiv) in MeCN (7 mL + 2 mL rinse). Purification by column chromatography (CH_2Cl_2/EtOAc; 9:1) gave γ-hydroxy vinyl sulfone (*S*)-**15** as an orange solid (178 mg, 49%). $[\alpha]_D$ = +49 (c = 1.0, $CHCl_3$); Lit.[5c] $[\alpha]_D$ = +45.3 (c = 1.0, $CHCl_3$). HPLC analysis (Chiralcel OJ-H column) heptane/ethanol; 90:10 (1.0 mL/min): t_r major (*S*)-**15** = 17.2 min, t_r minor (*R*)-**15** = 18.5 min; 98% ee.

(*R*,*E*)-5-Phenyl-1-(phenylsulfonyl)pent-1-en-3-ol (*R*)-16. AO flask: 4-Phenylbutanal[23] **12** (518 mg, 3.50 mmol, 1.2 equiv), nitrosobenzene (312 mg, 2.91 mmol, 1.0 equiv), and L-proline (68 mg, 0.59 mmol, 0.2 equiv) in MeCN (14 mL) were stirred for 2 h at 0 °C. HWE flask: Diethyl [(phenylsulfonyl)methyl]phosphonate **8** (1.71 g, 5.85 mmol, 2.0 equiv), LiBr (527 mg, 6.07 mmol, 2.1 equiv), and Et_3N (0.82 mL, 5.88 mmol, 2.0 equiv) in MeCN (10 mL + 4 mL rinse). After aqueous workup, purification by column chromatography (CH_2Cl_2/EtOAc; 9:1) gave γ-hydroxy vinyl sulfone (*R*)-**16** as a powdery yellow solid (383 mg, 43%). Mp 92−96 °C. R_f = 0.4 (CH_2Cl_2/EtOAc; 9:1). IR (film): ν_{max} 3444, 3057, 2933, 1626, 1446, 1397, 1299, 1282, 1145, 1102, 1086, 1023 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.80−1.91 (m, 2H, OH + CH_2), 1.95 (dddd, J = 13.5, 9.0, 7.0, 4.5 Hz, 1H CH_2), 2.68−2.80 (m, 2H, CH_2), 4.34−4.41 (m, 1H, CH), 6.61 (dd, J = 15.0, 2.0 Hz, 1H, CH), 7.00 (dd, J = 15.0, 4.0 Hz, 1H, CH), 7.16 (d, J = 7.0 Hz, 2H, ArH), 7.20 (t, J = 7.0 Hz, 1H, ArH), 7.29 (t, J = 7.0 Hz, 2H, ArH), 7.54 (t, J = 7.5 Hz, 2H, ArH), 7.62 (t, J = 7.5 Hz, 1H, ArH), 7.87 (d, J = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.4 (CH_2), 37.6 (CH_2), 69.5 (CH), 126.2 (CH), 127.7 (CH), 128.4 (CH), 128.6 (CH), 129.3 (CH), 129.9 (CH), 133.5 (CH), 140.2 (C), 140.7 (C), 147.9 (CH) ppm. HRMS (ES^+): $C_{17}H_{18}O_3NaS$ (MNa^+) calcd 325.0874; found 325.0888. $[\alpha]_D$ = −38 (c = 1.0, $CHCl_3$). Anal. calcd $C_{17}H_{18}O_3S$: C, 67.52; H, 6.00; found C, 67.73; H, 5.93. HPLC analysis (Chiralcel OJ-H column) heptane/ethanol; 80:20 (1.0 mL/min): t_r major (*R*)-**16** = 22.2 min, t_r minor (*S*)-**16** = 31.3 min; 97% ee.

(*S*,*E*)-5-Phenyl-1-(phenylsulfonyl)pent-1-en-3-ol (*S*)-16. AO flask: 4-Phenylbutanal[23] **12** (505 mg, 3.41 mmol, 1.2 equiv), nitrosobenzene (307 mg, 2.87 mmol, 1.0 equiv), and D-proline (66 mg, 0.57 mmol, 0.2 equiv) in MeCN (14 mL) were stirred for 2 h at 0 °C. HWE flask: Diethyl [(phenylsulfonyl)methyl]phosphonate **8** (1.66 g, 5.68 mmol, 2.0 equiv), LiBr (501 mg, 5.77 mmol, 2.0 equiv), and Et_3N (0.80 mL, 5.74 mmol, 2.0 equiv) in MeCN (10 mL + 4 mL rinse). After aqueous workup, purification by column chromatography (CH_2Cl_2/EtOAc; 9:1) gave γ-hydroxy vinyl sulfone (*S*)-**16** as a powdery yellow solid (332 mg, 38%). $[\alpha]_D$ = +50 (c = 1.0, $CHCl_3$). HPLC analysis (Chiralcel OJ-H column) heptane/ethanol; 80:20 (1.0 mL/min): t_r minor (*R*)-**16** = 22.2 min, t_r major (*S*)-**16** = 30.9 min; 96% ee.

***tert*-Butyl (6-Oxohexyl)carbamate 13.**[24] Under nitrogen, at room temperature, to a stirred solution of *tert*-butyl (6-hydroxyhexyl)-carbamate[25] (1.65 g, 7.59 mmol, 1.0 equiv) and TEMPO (120 mg, 0.77 mmol, 0.1 equiv) in CH_2Cl_2 (35 mL) was added BAIB (2.70 g, 8.38 mmol, 1.1 equiv), and the reaction was monitored by TLC. After 4 h stirring, a further portion of TEMPO (127 mg, 0.81 mmol, 0.1 equiv) was added followed by a further portion of BAIB (546 mg, 1.70 mmol, 0.2 equiv) to drive the reaction to completion. After a further 3 h stirring, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and quenched with sodium thiosulfate sat. aq. solution (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with $NaHCO_3$ sat. aq. solution (50 mL), brine (50 mL), dried over $MgSO_4$, and filtered, and solvent was removed in vacuo to give the crude product. Purification by column chromatography (CH_2Cl_2 → CH_2Cl_2/EtOAc; 9:1) gave aldehyde **13** as a pale clear orange/yellow oil (0.92 g, 56%). R_f = 0.4 (CH_2Cl_2/EtOAc; 9:1). Data is consistent with that reported in the literature.[24]

(*R*,*E*)-*tert*-Butyl [5-Hydroxy-7-(phenylsulfonyl)hept-6-en-1-yl]carbamate (*R*)-17. AO flask: *tert*-Butyl (6-oxohexyl)carbamate **13** (689 mg, 3.20 mmol, 1.2 equiv), nitrosobenzene (286 mg, 2.67 mmol, 1.0 equiv), and L-proline (66 mg, 0.57 mmol, 0.2 equiv) in MeCN (16 mL) were stirred for 2 h at 0 °C. HWE flask: Diethyl [(phenylsulfonyl)methyl]phosphonate **8** (1.56 g, 5.34 mmol, 2.0 equiv), LiBr (469 mg, 5.40 mmol, 2.0 equiv), and Et_3N (0.75 mL, 5.38 mmol, 2.0 equiv) in MeCN (12 mL + 4 mL rinse). After aqueous workup, purification by column chromatography (*c*-Hex/EtOAc; 1:1) gave γ-hydroxy vinyl sulfone (*R*)-**17** as an orange oil which gradually solidified as an orange crystalline solid (415 mg, 42%). Mp 68−72 °C. R_f = 0.2 (*c*-Hex/EtOAc; 1:1) IR (film): ν_{max} 3388, 2977, 1689, 1523, 1447, 1367, 1306, 1146, 1086 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.35−1.53 (m, 13H, CH_2 + CH_3), 1.54−1.62 (m, 1H, CH_2), 1.63−1.75 (m, 1H, CH_2), 2.64 (s (br), 1H, OH), 3.07−3.14 (m, 2H, CH_2), 4.35−4.41 (m, 1H, CH), 4.60 (s (br), 1H, NH), 6.62 (dd, J = 15.0, 2.0 Hz, 1H, CH), 6.97 (dd, J = 15.0, 3.5 Hz, 1H, CH), 7.54 (t, J = 7.5 Hz, 2H, ArH), 7.62 (t, J = 7.5 Hz, 1H, ArH), 7.88 (d, J = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7 (CH_2), 28.4 (CH_3), 29.9 (CH_2), 35.4 (CH_2), 39.7 (CH_2), 70.0 (CH), 79.4 (C), 127.7 (CH), 129.3 (CH), 129.8 (CH), 133.4 (CH), 140.4 (C), 148.0 (CH), 156.4 (CO) ppm. HRMS (ES^+): $C_{18}H_{27}NO_5NaS$ (MNa^+) calcd 392.1508; found 392.1490. $[\alpha]_D$ = −18 (c = 1.0, $CHCl_3$). Anal. calcd $C_{18}H_{27}NO_5S$: C, 58.51; H, 7.37; N, 3.79; found C, 58.34; H, 7.29; N, 3.61. HPLC analysis (Chiralcel IA column) heptane/ethanol; 80:20 (1.0 mL/min): t_r minor (*S*)-**17** = 13.1 min, t_r major (*R*)-**17** = 15.1 min; 98% ee.

(*S*,*E*)-*tert*-Butyl [5-Hydroxy-7-(phenylsulfonyl)hept-6-en-1-yl]carbamate (*S*)-17. AO flask: *tert*-Butyl (6-oxohexyl)carbamate **13** (265 mg, 1.23 mmol, 1.2 equiv), nitrosobenzene (111 mg, 1.04 mmol, 1.0 equiv), and D-proline (26 mg, 0.23 mmol, 0.2 equiv) in MeCN (6 mL) were stirred for 2 h at 0 °C. HWE flask: Diethyl [(phenylsulfonyl)methyl]phosphonate **8** (595 mg, 2.04 mmol, 2.0 equiv), LiBr (190 mg, 2.19 mmol, 2.1 equiv), and Et_3N (0.29 mL, 2.08 mmol, 2.0 equiv) in MeCN (5 mL + 1 mL rinse). After aqueous workup, purification by column chromatography (*c*-Hex/EtOAc; 1:1) gave γ-hydroxy vinyl sulfone (*S*)-**17** as an orange oil which gradually solidified as an orange crystalline solid (144 mg, 38%). $[\alpha]_D$ = +18 (c = 1.0, $CHCl_3$). HPLC analysis (Chiralcel IA column) heptane/ethanol; 80:20 (1.0 mL/min): t_r major (*S*)-**17** = 13.0 min, t_r minor (*R*)-**17** = 15.1 min; 98% ee.

(*R*)-5-Phenylpent-1-en-3-ol (*R*)-18.[26] At room temperature, to a vigorously stirred solution of vinyl sulfone (*R*)-**16** (86 mg, 0.28 mmol, 1.0 equiv) in MeOH (1.7 mL) was added oven activated magnesium turnings (26 mg, 1.07 mmol, 3.8 equiv) followed by $HgCl_2$ (a small

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spatula tip). The resulting green/black mixture was stirred for 3 h and quenched with sat. aq. NH_4Cl solution (5 mL). The mixture was extracted with Et_2O (2 × 10 mL), and the combined ethereal layers were washed with brine (10 mL), dried over $MgSO_4$, and filtered, and solvent was removed in vacuo to give the crude product. Purification by column chromatography (CH_2Cl_2) gave allylic alcohol (*R*)-**18** as a clear light yellow liquid (24 mg, 52%). R_f = 0.5 (CH_2Cl_2). IR (film): ν_{max} 3362, 2927, 1603, 1496, 1454, 1041, 991 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.56 (s (br), 1H, OH), 1.80−1.92 (m, 2H, CH_2), 2.65−2.79 (m, 2H, CH_2), 4.13 (app. q, *J* = 6.0 Hz, 1H, CH), 5.14 (d, *J* = 10.5 Hz, 1H, CH_2), 5.25 (d, *J* = 17.0 Hz, 1H, CH_2), 5.90 (ddd, *J* = 17.0, 10.5, 6.0 Hz, 1H, CH), 7.16−7.23 (m, 3H, ArH), 7.25−7.31 (m, 2H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.6 (CH_2), 38.5 (CH_2), 72.5 (CH), 114.9 (CH_2), 125.8 (CH), 128.39 (CH), 128.44 (CH), 141.0 (CH), 141.8 (C) ppm. $[\alpha]_D$ = +7 (*c* = 1.0, $CHCl_3$). Lit.[26a] $[\alpha]_D$ = −5.8 (*c* = 1.3, $CHCl_3$).

(*S*)-5-Phenylpent-1-en-3-ol (*S*)-18.[26] In a procedure identical to the above desulfonylation: Vinyl sulfone (*S*)-**16** (101 mg, 0.33 mmol, 1.0 equiv), MeOH (2 mL), oven activated magnesium turnings (25 mg, 1.03 mmol, 3.1 equiv), and $HgCl_2$ (a small spatula tip). After aqueous workup, purification by column chromatography (CH_2Cl_2) gave allylic alcohol (*S*)-**18** as a clear light yellow liquid (27 mg, 50%). $[\alpha]_D$ = −6 (*c* = 1.0, $CHCl_3$), Lit.[26b] $[\alpha]_D$ = +4.9 (*c* = 2.2, $CHCl_3$). Note: Some ambiguity concerning absolute stereochemistry[26a−c] for correct assignment, see Helmchen and co-workers.[26d]

(*R*)-1-Phenyl-5-(phenylsulfonyl)pentan-3-ol (*R*)-19. Vinyl sulfone (*R*)-**16** (61 mg, 0.20 mmol, 1.0 equiv) was stirred with 10% w/w Pd/C (22 mg, 0.021 mmol, 0.1 equiv) in EtOH (6 mL) under an atmosphere of hydrogen (1 atm.) for 24 h. The reaction mixture was filtered through Celite, and the cake washed with EtOAc (3 × 10 mL). Solvent was removed in vacuo to give the alkane compound (*R*)-**19** as a white powdery solid (61 mg, > 95%). Mp 108−111 °C. R_f = 0.4 (CH_2Cl_2/EtOAc; 9:1). IR (film): ν_{max} 3305, 2929, 1445, 1305, 1265, 1148, 1082, 1039 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.72−1.85 (m, 4H, CH_2 + OH), 1.97 (dddd, *J* = 13.5, 9.5, 6.0, 3.5 Hz, 1H, CH_2), 2.65 (dt, *J* = 14.0, 8.0 Hz, 1H, CH_2), 2.75 (dt, *J* = 14.0, 7.5 Hz, 1H, CH_2), 3.20 (ddd, *J* = 14.0, 10.0, 6.0 Hz, 1H, CH_2), 3.30 (ddd, *J* = 14.0, 10.0, 5.0 Hz, 1H, CH_2), 3.72 (app. dtd, *J* = 9.5, 6.0, 3.5 Hz, 1H, CH), 7.16 (d, *J* = 7.0 Hz, 2H, ArH), 7.19 (t, *J* = 7.0 Hz, 1H, ArH) 7.25−7.29 (m, 2H, ArH), 7.56 (t, *J* = 7.5 Hz, 2H, ArH), 7.65 (t, *J* = 7.5 Hz, 1H, ArH), 7.90 (d, *J* = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.1 (CH_2), 31.9 (CH_2), 39.0 (CH_2), 53.0 (CH_2), 69.3 (CH), 126.0 (CH), 128.0 (CH), 128.3 (CH), 128.5 (CH), 129.3 (CH), 133.7 (CH), 139.1 (C), 141.3 (C) ppm. HRMS (ES^+): $C_{17}H_{20}O_3NaS$ (MNa^+) calcd 327.1031; found 327.1034. $[\alpha]_D$ = −10 (*c* = 1.0, $CHCl_3$).

(*S*)-1-Phenyl-5-(phenylsulfonyl)pentan-3-ol (*S*)-19. In a procedure identical to the above hydrogenation: Vinyl sulfone (*S*)-**16** (63 mg, 0.21 mmol, 1.0 equiv), 10% w/w Pd/C (22 mg, 0.02 mmol, 0.1 equiv) in EtOH (6 mL) under an atmosphere of hydrogen (1 atm.) for 24 h. The product (*S*)-**19** was isolated as a white powdery solid (63 mg, >95%). $[\alpha]_D$ = +9 (*c* = 1.0, $CHCl_3$).

(*R,E*)-1-(Phenylsulfonyl)non-1-en-3-yl Methanesulfonate. At 0 °C, under nitrogen, to a stirred solution of alcohol (*R*)-*E*-**9** (101 mg, 0.36 mmol, 1.0 equiv) and Et_3N (0.20 mL, 1.43 mmol, 4.0 equiv) in CH_2Cl_2 (4 mL) was added MsCl (0.11 mL, 1.42 mmol, 4.0 equiv) in a dropwise fashion, and the reaction mixture was stirred overnight warming gradually to room temperature. The reaction mixture was quenched with 1 M HCl (5 mL), and the layers were separated. The aqueous layer was back-extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were washed with brine (10 mL). The organic layer was dried over $MgSO_4$ and filtered, and solvent was removed in vacuo to give the crude product. Purification by column chromatography (CH_2Cl_2) gave (*R,E*)-1-(phenylsulfonyl)non-1-en-3-yl methanesulfonate as a clear pale yellow oil (109 mg, 85%). R_f = 0.2 (CH_2Cl_2). IR (film): ν_{max} 3062, 2931, 2859, 1638, 1447, 1321, 1175, 1149, 1087, 970, 914 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.5 Hz, 3H, CH_3), 1.21−1.44 (m, 8H, CH_2), 1.73−1.86 (m, 2H, CH_2), 2.99 (s, 3H, CH_3), 5.23 (app. q, *J* = 5.5 Hz, 1H, CH), 6.63 (d, *J* = 15.0 Hz, 1H, CH), 6.93 (dd, *J* = 15.0, 5.5 Hz, 1H, CH), 7.57 (t, *J* = 7.5 Hz, 2H, ArH), 7.65 (t, *J* = 7.5 Hz, 1H, ArH), 7.89 (d, *J* = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5 (CH_2), 24.5 (CH_2), 28.7 (CH_2), 31.4 (CH_2), 34.5 (CH_2), 38.9 (CH_3), 78.6 (CH), 127.8 (CH), 129.5 (CH), 132.7 (CH), 133.8 (CH), 139.6 (C), 141.4 (CH) ppm. HRMS (ES^+): $C_{16}H_{24}O_5NaS_2$ (MNa^+) calcd 383.0963; found 383.0954. $[\alpha]_D$ = +10 (*c* = 1.0, $CHCl_3$). Anal. calcd $C_{16}H_{24}O_5S_2$: C, 53.31; H, 6.71; found C, 53.41; H, 6.60.

(*S,E*)-1-(Phenylsulfonyl)non-1-en-3-yl Methanesulfonate. In a procedure identical to the above mesylation: Alcohol (*S*)-*E*-**9** (232 mg, 0.82 mmol, 1.0 equiv), Et_3N (0.46 mL, 3.30 mmol, 4.0 equiv), and MsCl (0.26 mL, 3.36 mmol, 4.1 equiv) in CH_2Cl_2 (8 mL). After aqueous workup, purification by column chromatography (CH_2Cl_2) gave (*S,E*)-1-(Phenylsulfonyl)non-1-en-3-yl methanesulfonate as a clear pale yellow oil (267 mg, 90%). $[\alpha]_D$ = −10 (*c* = 1.0, $CHCl_3$).

(*S,E*)-[(3-Azidonon-1-en-1-yl)sulfonyl]benzene (*S*)-20. At 0 °C, to a stirred solution of mesylate (*R*)-**S1** (249 mg, 0.69 mmol, 1.0 equiv) in DMF (7 mL) was added sodium azide (93 mg, 1.43 mmol, 2.1 equiv). Stirring was continued for 3 h at 0 °C after which time water (5 mL) was added to the flask, and the mixture was extracted with Et_2O (3 × 15 mL). The combined ethereal layers were washed with brine (15 mL), dried over $MgSO_4$, and filtered, and solvent was removed in vacuo to give the crude product. Purification by column chromatography (CH_2Cl_2) gave azide (*S*)-**20** as a clear colorless liquid (169 mg, 80%). Note: the allylic azides were found to isomerize/oligomerize/polymerize over time and were therefore used soon after preparation or stored under nitrogen in a freezer at −20 °C. R_f = 0.7 (CH_2Cl_2). IR (film): ν_{max} 2930, 2859, 2108, 1447, 1322, 1149, 1086 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.5 Hz, 3H, CH_3), 1.21−1.44 (m, 8H, CH_2), 1.66 (app. q, *J* = 7.5 Hz, 2H, CH_2), 4.10 (app. q, *J* = 6.5 Hz, 1H, CH), 6.57 (d, *J* = 15.0 Hz, 1H, CH), 6.86 (dd, *J* = 15.0, 5.5 Hz, 1H, CH), 7.56 (t, *J* = 7.5 Hz, 2H, ArH), 7.65 (t, *J* = 7.5 Hz, 1H, ArH), 7.90 (d, *J* = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5 (CH_2), 25.4 (CH_2), 28.8 (CH_2), 31.5 (CH_2), 33.8 (CH_2), 61.5 (CH), 127.7 (CH), 129.4 (CH), 132.2 (CH), 133.7 (CH), 139.9 (C), 142.8 (CH) ppm. HRMS (ES^+): $C_{15}H_{21}N_3O_2NaS$ (MNa^+) calcd 330.1252; found 330.1260. $[\alpha]_D$ = +11 (*c* = 1.0, $CHCl_3$). Anal. calcd $C_{15}H_{21}N_3O_2S$: C, 58.61; H, 6.89; N, 13.67; found C, 58.48; H, 6.83; N, 13.62.

(*R,E*)-[(3-Azidonon-1-en-1-yl)sulfonyl]benzene (*R*)-20. In a procedure identical to the above azide displacement: Mesylate (*S*)-**S1** (242 mg, 0.67 mmol, 1.0 equiv), sodium azide (90 mg, 1.38 mmol, 2.1 equiv) in DMF (7 mL). After aqueous workup, purification by column chromatography (CH_2Cl_2) gave azide (*R*)-**20** as clear colorless oil (168 mg, 81%). $[\alpha]_D$ = −14 (*c* = 1.0, $CHCl_3$).

(*S,E*)-[3-Azido-5-(phenylsulfonyl)pent-4-en-1-yl]benzene (*S*)-21. In a procedure identical to the above mesylation: Alcohol (*R*)-**16** (265 mg, 0.88 mmol, 1.0 equiv), Et_3N (0.49 mL, 3.52 mmol, 4.0 equiv), and MsCl (0.27 mL, 3.49 mmol, 4.0 equiv) in CH_2Cl_2 (9 mL). After aqueous workup, purification by column chromatography (CH_2Cl_2) gave the intermediate mesylate as a yellow viscous oil which crystallized over 3 h as a pale yellow crystalline solid (300 mg, 90%). R_f = 0.2 (CH_2Cl_2). In a procedure identical to the above azide displacement: The intermediate mesylate (300 mg, 0.79 mmol, 1.0 equiv), sodium azide (106 mg, 1.63 mmol, 2.1 equiv) in DMF (8 mL). After aqueous workup, purification by column chromatography (*c*-Hex/CH_2Cl_2; 1:9) gave azide (*S*)-**21** as clear viscous colorless oil which crystallized overnight as a white crystalline solid (231 mg, 89%). Mp 70−74 °C. R_f = 0.6 (CH_2Cl_2). IR (film): ν_{max} 2924, 2106, 1447, 1321, 1148, 1086 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.95 (app. q, *J* = 7.5 Hz, 2H, CH_2), 2.69 (dd, *J* = 14.5, 8.0 Hz, 1H, CH_2), 2.75 (dd, *J* = 14.5, 7.0 Hz, 1H, CH_2), 4.06 (app. q, *J* = 6.0 Hz, 1H, CH), 6.57 (d, *J* = 15.0 Hz, 1H, CH), 6.87 (dd, *J* = 15.0, 6.0 Hz, 1H, CH), 7.15 (d, *J* = 7.5 Hz, 2H, ArH), 7.21 (t, *J* = 7.5 Hz, 1H, ArH), 7.29 (t, *J* = 7.5 Hz, 2H, ArH), 7.55 (t, *J* = 7.5 Hz, 2H, ArH), 7.64 (t, *J* = 7.5 Hz, 1H, ArH), 7.89 (d, *J* = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.6 (CH_2), 35.3 (CH_2), 60.6 (CH), 126.5 (CH), 127.8 (CH), 128.4 (CH), 128.7 (CH), 129.4 (CH), 132.6 (CH), 133.7 (CH), 139.81 (C), 139.84 (C), 142.3 (CH) ppm. HRMS (ES^+): $C_{17}H_{17}N_3O_2NaS$ (MNa^+) calcd 350.0939; found 350.0955. $[\alpha]_D$ = +1 (*c* = 1.0, $CHCl_3$). Anal. calcd $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N,

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12.83; found C, 62.15; H, 5.03; N, 12.68. Crystals suitable for single crystal X-ray diffraction were grown from the slow evaporation of a CH_2Cl_2 solution of (*S*)-**21**.

(*R*,*E*)-[3-Azido-5-(phenylsulfonyl)pent-4-en-1-yl]benzene (*R*)-21. In a procedure identical to the above mesylation: Alcohol (*S*)-**16** (260 mg, 0.86 mmol, 1.0 equiv), Et_3N (0.48 mL, 3.44 mmol, 4.0 equiv), and MsCl (0.27 mL, 3.49 mmol, 4.1 equiv) in CH_2Cl_2 (9 mL). After aqueous workup, purification by column chromatography (CH_2Cl_2) gave the intermediate mesylate as a yellow viscous oil which crystallized over 3 h as a pale yellow crystalline solid (313 mg, >95%). R_f = 0.2 (CH_2Cl_2). In a procedure identical to the above azide displacement: The intermediate mesylate (313 mg, 0.82 mmol, 1.0 equiv), sodium azide (108 mg, 1.66 mmol, 2.0 equiv) in DMF (8 mL). After aqueous workup, purification by column chromatography (*c*-Hex/CH_2Cl_2; 1:9) gave azide (*R*)-**21** as clear viscous colorless oil which crystallized overnight as a white crystalline solid (219 mg, 81%). $[\alpha]_D$ = −1 (*c* = 1.0, $CHCl_3$).

(*S*,*E*)-*tert*-Butyl [5-Azido-7-(phenylsulfonyl)hept-6-en-1-yl]carbamate (*S*)-22. In a procedure identical to the above mesylation: Alcohol (*R*)-**17** (112 mg, 0.30 mmol, 1.0 equiv), Et_3N (0.19 mL, 1.36 mmol, 4.5 equiv), and MsCl (0.10 mL, 1.29 mmol, 4.3 equiv) in CH_2Cl_2 (3 mL). After aqueous workup, purification by column chromatography (CH_2Cl_2/EtOAc; 9:1) gave the intermediate mesylate as a viscous yellow oil which crystallized gradually over time as a yellow crystalline solid (116 mg, 86%). R_f = 0.2 (CH_2Cl_2/EtOAc; 9:1). In a procedure identical to the above azide displacement: The intermediate mesylate (116 mg, 0.26 mmol, 1.0 equiv), sodium azide (35 mg, 0.54 mmol, 2.1 equiv) in DMF (2.5 mL). After aqueous workup, purification by column chromatography (CH_2Cl_2/EtOAc; 9:1) gave azide (*S*)-**22** as clear colorless liquid (94 mg, 92%). R_f = 0.5 (CH_2Cl_2/EtOAc; 9:1). IR (film): ν_{max} = 3392, 2977, 2934, 2109, 1703, 1518, 1447, 1366, 1149, 1086 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.35−1.55 (m, 13H, CH_2 + CH_3), 1.61−1.74 (m, 2H, CH_2), 3.06−3.16 (m, 2H, CH_2), 4.10 (app. q, *J* = 6.0 Hz, 1H, CH), 4.52 (s (br), 1H, NH), 6.58 (d, *J* = 15.0 Hz, 1H, CH), 6.85 (15.0, 5.5 Hz, 1H, CH), 7.57 (t, *J* = 7.5 Hz, 2H, ArH), 7.65 (t, *J* = 7.5 Hz, 1H, ArH), 7.90 (d, *J* = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.8 (CH_2), 28.4 (CH_3), 29.7 (CH_2), 33.5 (CH_2), 40.2 (CH_2), 61.5 (CH), 79.3 (C), 127.8 (CH), 129.4 (CH), 132.5 (CH), 133.7 (CH), 139.9 (C), 142.4 (CH), 155.9 (CO) ppm. HRMS (ES^+) $C_{18}H_{26}N_4O_4NaS$ (MNa^+) calcd 417.1572; found 417.1552. $[\alpha]_D$ = +25 (*c* = 2.0, $CHCl_3$). Anal. calcd $C_{18}H_{26}N_4O_4S$: C, 54.80; H, 6.64; N, 14.20; found C, 54.58; H, 6.61; N, 13.80.

(*R*,*E*)-*tert*-Butyl [5-Azido-7-(phenylsulfonyl)hept-6-en-1-yl]carbamate (*R*)-22. In a procedure identical to the above mesylation: Alcohol (*S*)-**17** (110 mg, 0.30 mmol, 1.0 equiv), Et_3N (0.19 mL, 1.36 mmol, 4.5 equiv), and MsCl (0.10 mL, 1.29 mmol, 4.3 equiv) in CH_2Cl_2 (3 mL). After aqueous workup, purification by column chromatography (CH_2Cl_2/EtOAc; 9:1) gave the intermediate mesylate as a viscous yellow oil which crystallized gradually over time as a yellow crystalline solid (109 mg, 82%). R_f = 0.2 (CH_2Cl_2/EtOAc; 9:1). In a procedure identical to the above azide displacement: The intermediate mesylate (109 mg, 0.24 mmol, 1.0 equiv), sodium azide (35 mg, 0.54 mmol, 2.2 equiv) in DMF (2.5 mL). After aqueous workup, purification by column chromatography (CH_2Cl_2/EtOAc; 9:1) gave azide (*R*)-**22** as clear colorless liquid (84 mg, 87%). $[\alpha]_D$ = −29 (*c* = 2.0, $CHCl_3$).

(*S*)-Benzyl (1-(Methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate.[27] At 0 °C, **24** (2.01 g, 6.72 mmol, 1.0 equiv) was stirred with DIPEA (1.4 mL, 8.04 mmol, 1.2 equiv) in CH_2Cl_2 (50 mL) for 10 min. DIC (1.05 mL, 6.71 mmol, 1.0 equiv) was added, and the mixture was stirred for 10 min. *N*,*O*-dimethylhydroxylamine hydrochloride (651 mg, 6.67 mmol, 1.0 equiv) was then added, and the reaction mixture was stirred overnight warming slowly to room temperature. The mixture was filtered, and the filtrate washed with 1 M HCl (20 mL), brine (20 mL), dried over $MgSO_4$, and filtered, and solvent was removed in vacuo to give the crude product. Purification by column chromatography (*c*-Hex/EtOAc; 2:1) gave the Weinreb amide (1.84 g, 80%) as a golden syrup. R_f = 0.5 (*c*-Hex/EtOAc; 1:1). IR (film): ν_{max} = 3303, 2939, 1719, 1657, 1529, 1497, 1455, 1391, 1254, 1049 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.91 (dd, *J* = 13.5, 7.0 Hz, 1H, CH_2), 3.08 (dd, *J* = 13.5, 6.0 Hz, 1H, CH_2), 3.17 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 4.96−5.06 (m, 2H, CH_2 + CH), 5.09 (d, *J* = 12.5 Hz, 1H, CH_2), 5.44 (s (br), 1H, NH), 7.15 (d, *J* = 7.0 Hz, 2 H, ArH), 7.19−7.38 (m, 8H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.1 (CH_3), 38.7 (CH_2), 52.1 (CH), 61.5 (CH_3), 66.8 (CH_2), 126.9 (CH), 128.0 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 129.4 (CH), 136.26 (C), 136.35 (C), 155.8 (CO), 171.9 (CO) ppm. HRMS (ES^+) $C_{19}H_{22}N_2O_4Na$ (MNa^+) calcd 365.1477; found 365.1469. $[\alpha]_D$ = +20 (*c* = 0.1, CH_2Cl_2).

(*S*)-Benzyl (1-Oxo-3-phenylpropan-2-yl)carbamate.[28] Under nitrogen, at −78 °C, to a vigorously stirred solution of $LiAlH_4$ (2.37 g, 62.5 mmol, 5.0 equiv) in dry THF (60 mL) was added the above Weinreb amide (4.29 g, 12.5 mmol, 1.0 equiv) as a solution in dry THF (20 mL) rapidly via syringe. The mixture was stirred for 5 min after which a pressure equalizing dropping funnel with 1 M $KHSO_4$ (20 mL) was attached to the flask. Cautiously, this solution was added one drop at a time (under nitrogen) until excess $LiAlH_4$ was consumed, after which the rest of the contents of the dropping funnel were added over 5 min. Water was then added (30 mL) followed by EtOAc (100 mL), and the solution was warmed to room temperature stirring vigorously. The contents of the flask were transferred to a separating funnel, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with 1 M HCl (2 × 50 mL), sat. aq. $NaHCO_3$ (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$ and filtered, and solvent was removed in vacuo to give aldehyde (3.45 g, > 95%) as a white solid. Mp = 70−73 °C. R_f = 0.2 (*c*-Hex/EtOAc; 3:1). IR (film): ν_{max} = 3336, 3032, 2953, 2864, 1741, 1690, 1537, 1453, 1263, 1064 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.13 (d, *J* = 6.5 Hz, 2H, CH_2), 4.50 (app. q, *J* = 6.5 Hz, 1H, CH), 5.10 (s, 2H, CH_2), 5.32 (d, *J* = 6.5 Hz, 1H, NH), 7.13 (d, *J* = 7.0 Hz, 2H, ArH), 7.21−7.39 (m, 8H, ArH), 9.62 (s, 1H, CHO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.5 (CH_2), 61.2 (CH), 67.2 (CH_2), 127.3 (CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 128.9 (CH), 129.4 (CH), 135.5 (C), 136.2 (C), 156.0 (CO), 198.9 (CHO) ppm. HRMS (ES^+) $C_{17}H_{17}NO_3Na$ (MNa^+) calcd 306.1106; found 306.1111. $[\alpha]_D$ = +29 (*c* = 0.1, CH_2Cl_2).

(*S*)-Benzyl (4,4-dibromo-1-phenylbut-3-en-2-yl)carbamate. Under N_2 at room temperature, CBr_4 (2.01 g, 6.06 mmol, 2.0 equiv) was stirred in anhydrous CH_2Cl_2 (20 mL). To this was added Ph_3P (3.20 g, 12.20 mmol, 4.0 equiv), and the red solution was stirred for 10 min. The above aldehyde (856 mg, 3.02 mmol, 1.0 equiv) was added as a solution in dry CH_2Cl_2 (10 mL) to give a deep burgundy colored solution. TLC analysis confirmed consumption of starting material after 1 min after which silica was added to the flask, solvent was removed in vacuo (30 °C water bath temperature), and the material was purified by column chromatography (*c*-Hex/EtOAc; 7:1) to give dibromide (701 mg, 53%) as a white crystalline solid. Note: the success of this reaction depends on the strict short reaction time after addition of the aldehyde. Longer reaction times lead to substantial decomposition and diminished yields. Mp = 103−107 °C R_f = 0.5 (*c*-Hex/EtOAc; 3:1). IR (film): ν_{max} = 3330, 2928, 1692, 1535, 1453, 1441, 1343, 1264, 1232, 1083, 1042, 1022, 803, 743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.92 (d, *J* = 5.5 Hz, 2H, CH_2), 4.56 (app. p, *J* = 7.5 Hz, 1H, CH), 4.81 (s (br), 1H, NH), 5.08 (s, 2H, CH_2), 6.40 (d, *J* = 7.5 Hz, 1H, CH), 7.13−7.18 (m, 2H, ArH), 7.22−7.39 (m, 8H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.6 (CH_2), 54.9 (CH), 66.9 (CH_2), 91.6 (CBr_2), 127.0 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 128.7 (CH), 129.5 (CH), 136.0 (C), 136.2 (C), 137.9 (CH), 155.3 (CO) ppm. HRMS (ES^+) $C_{18}H_{17}NO_2Na^{79}Br^{81}Br$ (MNa^+) calcd 461.9503; found 461.9524. $[\alpha]_D$ = +12 (*c* = 0.1, CH_2Cl_2).

(*S*)-Benzyl (1-Phenylbut-3-yn-2-yl)carbamate 23. Under nitrogen, at −78 °C, to a stirred solution of the above dibromide (230 mg, 0.52 mmol, 1.0 equiv) in dry THF (5 mL) was added freshly titrated[29] *n*-BuLi in hexanes (1.53 M, 1.1 mL, 1.68 mmol, 3.2 equiv) dropwise over 10 min after which time the reaction mixture went black. The reaction mixture was then warmed to 0 °C and stirred at for 30 min. The reaction mixture was then quenched with water (10 mL) and

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extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered, and solvent was removed in vacuo to give the crude product. Purification by column chromatography (*c*-Hex/EtOAc; 7:1) gave alkyne **23** as a white waxy solid (94 mg, 64%). Mp = 61−64 °C. R_f = 0.4 (*c*-Hex/EtOAc; 3:1). IR (film): ν_{max} = 3405, 3296, 3032, 2931, 1701, 1524, 1497, 1455, 1335, 1283, 1246, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.30 (d, *J* = 2.5 Hz, 1H, CH), 2.96 (dd, *J* = 13.5, 7.0 Hz, 1H, CH_2), 3.02 (dd, *J* = 13.5, 5.5 Hz, 1H, CH_2), 4.70−4.82 (m, 1H, CH), 4.92 (s (br), 1H, NH), 5.10 (s, 2H, CH_2), 7.20−7.39 (m, 10H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.5 (CH_2), 44.3 (CH), 67.0 (CH_2), 72.6 (CH), 82.4 (C), 127.0 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 129.8 (CH), 136.0 (C), 136.2 (C), 155.2 (CO), ppm. HRMS (ES^+) $C_{18}H_{17}NO_2Na$ (MNa^+) calcd 302.1157; found 302.1148. $[\alpha]_D$ = −25 (*c* = 0.1, CH_2Cl_2). Anal. calcd $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01; found C, 77.02, H, 6.31, N, 4.73.

Benzyl [(*S*)-2-Phenyl-1-(1-((*S*,*E*)-5-phenyl-1-(phenylsulfonyl)-pent-1-en-3-yl)-1*H*-1,2,3-triazol-4-yl)ethyl]carbamate 25. To a stirred solution of azide (*S*)-**21** (30 mg, 0.09 mmol, 1.0 equiv), alkyne **23** (27 mg, 0.10 mmol, 1.05 equiv), and $CuSO_4·5H_2O$ (6 mg, 0.02 mmol, 0.25 equiv) in DMF (1 mL) was added sodium ascorbate (14 mg, 0.07 mmol, 0.75 equiv), and the green reaction mixture was stirred for 3 days at room temperature. Solvent was removed in vacuo, and the residue was redissolved in EtOAc (10 mL) and washed with water (5 mL). The aqueous layer was back-extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and filtered, and solvent was removed in vacuo to give the crude product. Purification by column chromatography (*c*-Hex/EtOAc; 2:1) gave triazole **25** as a white powdery solid (42 mg, 76%). Mp 110−115 °C. R_f = 0.4 (*c*-Hex/EtOAc; 1:1). IR (film): ν_{max} = 3056, 2926, 1686, 1510, 1446, 1305, 1285, 1227, 1145, 1085 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.16−2.44 (m, 3H, CH_2), 2.45−2.54 (m, 1H, CH_2), 3.14 (dd, *J* = 13.0, 9.0 Hz, 1H, CH_2), 3.36 (dd, *J* = 13.0, 5.5 Hz, 1H, CH_2), 5.00−5.17 (m, 4H, CH + CH_2), 5.61 (d, *J* = 8.0 Hz, 1H, NH), 6.05 (d, *J* = 15.0 Hz, 1H, CH), 6.92−7.06 (m, 6H, CH + ArH), 7.15−7.24 (m, 5H, ArH), 7.28−7.37 (m, 6H, ArH), 7.53 (t, *J* = 7.5 Hz, 2H, ArH), 7.63 (t, *J* = 7.5 Hz, 1H, ArH), 7.80 (d, *J* = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.4 (CH_2), 35.4 (CH_2), 41.6 (CH_2), 49.3 (CH), 59.7 (CH), 66.9 (CH_2), 120.8 (CH), 126.7 (CH), 126.8 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 128.46 (CH), 128.53 (CH), 128.8 (CH), 129.4 (CH), 129.5 (CH), 132.7 (CH), 133.9 (CH), 136.3 (C), 137.0 (C), 138.9 (C), 139.3 (C), 141.9 (CH), 147.5 (C), 155.6 (CO) ppm. HRMS (ES^+) $C_{35}H_{34}N_4O_4NaS$ (MNa^+) calcd 629.2198; found 629.2180. $[\alpha]_D$ = +12 (*c* = 1.0, $CHCl_3$).

Benzyl [(*S*)-2-Phenyl-1-(1-((*R*,*E*)-5-phenyl-1-(phenylsulfonyl)-pent-1-en-3-yl)-1*H*-1,2,3-triazol-4-yl)ethyl]carbamate 26. In a procedure identical to the above click reaction: Azide (*R*)-**21** (30 mg, 0.09 mmol, 1.0 equiv), alkyne **23** (27 mg, 0.10 mmol, 1.05 equiv), $CuSO_4·5H_2O$ (6 mg, 0.02 mmol, 0.25 equiv), and sodium ascorbate (13 mg, 0.07 mmol, 0.7 equiv) in DMF (1 mL). After aqueous workup, purification by column chromatography (*c*-Hex/EtOAc; 2:1) gave triazole **26** as a white powdery solid (44 mg, 79%). Mp 157−161 °C. R_f = 0.4 (*c*-Hex/EtOAc; 1:1). IR (film): ν_{max} = 2925, 1713, 1518, 1454, 1315, 1245, 1148, 1085, 1043 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.17−2.28 (m, 1H, CH_2), 2.29−2.41 (m, 2H, CH_2), 2.44−2.54 (m, 1H, CH_2), 3.11 (dd, *J* = 13.5, 8.5 Hz, 1H, CH_2), 3.36 (dd, *J* = 13.5, 6.0 Hz, 1H, CH_2), 5.04−5.17 (m, 4H, CH + CH_2), 5.63 (d, *J* = 7.5 Hz, 1H, NH), 6.05 (dd, *J* = 15.0, 1.5 Hz, 1H, CH), 6.93−7.05 (m, 6H, CH + ArH), 7.11−7.23 (m, 4H, ArH), 7.26−7.38 (m, 7H, ArH), 7.52 (t, *J* = 7.5 Hz, 2H, ArH), 7.63 (t, *J* = 7.5 Hz, 1H, ArH), 7.80 (d, *J* = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.4 (CH_2), 35.3 (CH_2), 41.7 (CH_2), 49.3 (CH), 59.7 (CH), 66.9 (CH_2), 120.5 (CH), 126.7 (CH), 126.8 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 128.4 (2 × CH), 128.5 (CH), 128.8 (CH), 129.4 (CH), 129.5 (CH), 132.8 (CH), 133.9 (CH), 136.3 (C), 137.0 (C), 138.9 (C), 139.3 (C), 141.9 (CH), 147.6 (C), 155.6 (CO) ppm. HRMS (ES^+) $C_{35}H_{34}N_4O_4NaS$ (MNa^+) calcd 629.2198; found 629.2171. $[\alpha]_D$ = −21 (*c* = 1.0, $CHCl_3$).

Benzyl [(*S*)-1-(1-((*S*,*E*)-7-((*tert*-Butoxycarbonyl)amino)-1-(phenylsulfonyl)hept-1-en-3-yl)-1*H*-1,2,3-triazol-4-yl)-2-phenylethyl]carbamate 27. In a procedure identical to the above click reaction: Azide (*S*)-**22** (37 mg, 0.09 mmol, 1.0 equiv), alkyne **23** (27 mg, 0.09 mmol, 1.0 equiv), $CuSO_4·5H_2O$ (5 mg, 0.02 mmol, 0.2 equiv), and sodium ascorbate (12 mg, 0.06 mmol, 0.6 equiv) in DMF (1 mL). After aqueous workup, purification by column chromatography (*c*-Hex/EtOAc; 1:1) gave triazole **27** as a white powdery solid (47 mg, 74%). Mp 156−159 °C. R_f = 0.2 (*c*-Hex/EtOAc; 1:1). IR (film): ν_{max} = 3376, 3056, 2930, 1692, 1522, 1447, 1245, 1147, 1084, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.97−1.51 (m, 13H, CH_2 + CH_3), 1.91−2.07 (m, 2H, CH_2), 2.95−3.07 (m, 2H, CH_2), 3.11 (dd, *J* = 13.0, 8.5 Hz, 1H, CH_2), 3.34 (dd, *J* = 13.0, 6.0 Hz, 1H, CH_2), 4.51 (s (br), 1H, NH), 5.04−5.19 (m, 4H, CH_2 + CH), 5.62 (d, *J* = 7.0 Hz, 1H, NH), 6.07 (dd, *J* = 15.0, 1.5 Hz, 1H, CH), 6.97−7.05 (m, 4H, ArH + CH), 7.16−7.24 (m, 3H, ArH), 7.28−7.38 (m, 5H, ArH), 7.55 (t, *J* = 7.5 Hz, 2H, ArH), 7.65 (t, *J* = 7.5 Hz, 1H, ArH), 7.83 (d, *J* = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8 (CH_2), 28.4 (CH_3), 29.3 (CH_2), 33.6 (CH_2), 39.9 (CH_2), 41.6 (CH_2), 49.3 (CH), 60.8 (CH), 66.9 (CH_2), 79.3 (C), 120.3 (CH), 126.8 (CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 129.4 (CH), 129.5 (CH), 132.7 (CH), 133.9 (CH), 136.3 (C), 137.0 (C), 139.4 (C), 141.8 (CH), 147.6 (C), 155.6 (CO), 155.9 (CO) ppm. HRMS (ES^+) $C_{36}H_{43}N_5O_6NaS$ (MNa^+) calcd 696.2832; found 696.2824. $[\alpha]_D$ = +21 (*c* = 1.0, $CHCl_3$). Anal. calcd $C_{36}H_{43}N_5O_6S$: C, 64.17; H, 6.43; N, 10.39; found C, 63.93; H, 6.39; N, 10.27.

Benzyl [(*S*)-1-(1-((*R*,*E*)-7-((*tert*-Butoxycarbonyl)amino)-1-(phenylsulfonyl)hept-1-en-3-yl)-1*H*-1,2,3-triazol-4-yl)-2-phenylethyl]carbamate 28. In a procedure identical to the above click reaction: Azide (*R*)-**22** (38 mg, 0.10 mmol, 1.0 equiv), alkyne **23** (27 mg, 0.10 mmol, 1.0 equiv), $CuSO_4·5H_2O$ (5 mg, 0.02 mmol, 0.2 equiv), and sodium ascorbate (12 mg, 0.06 mmol, 0.6 equiv) in DMF (1 mL). After aqueous workup, purification by column chromatography (*c*-Hex/EtOAc; 1:1) gave triazole **28** as a white powdery solid (46 mg, 71%). Mp 97−106 °C. R_f = 0.2 (*c*-Hex/EtOAc; 1:1). IR (film): ν_{max} = 3356, 2932, 1707, 1521, 1448, 1366, 1250, 1149, 1086, 1043 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.00−1.24 (m, 2H, CH_2), 1.34−1.49 (m, 11H, CH_2 + CH_3), 1.91−2.05 (m, 2H, CH_2), 2.94−3.07 (m, 2H, CH_2), 3.10 (dd, *J* = 13.5, 8.0 Hz, 1H, CH_2), 3.34 (dd, *J* = 13.5, 6.0 Hz, 1H, CH_2), 4.53 (s (br), 1H, NH), 5.07 (d, *J* = 13.0, 1H, CH_2), 5.09−5.18 (m, 3H, CH_2 + CH), 5.64 (s (br), 1H, NH), 6.11 (d, *J* = 15.0 Hz, 1H, CH), 6.97−7.05 (m, 4H, CH + ArH), 7.14−7.24 (m, 3H, ArH), 7.28−7.38 (m, 5H, ArH), 7.54 (t, *J* = 7.5 Hz, 2H, ArH), 7.64 (t, *J* = 7.5 Hz, 1H, ArH), 7.82 (d, *J* = 7.5 Hz, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8 (CH), 28.4 (CH_3), 29.3 (CH_2), 33.5 (CH_2), 39.9 (CH_2), 41.6 (CH_2), 49.3 (CH), 60.7 (CH), 66.8 (CH_2), 79.3 (C), 120.2 (CH), 126.7 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 129.4 (CH), 129.5 (CH), 132.8 (CH), 133.9 (CH), 136.3 (C), 137.0 (C), 139.3 (C), 141.8 (CH), 147.7 (C), 155.6 (CO), 155.9 (CO) ppm. HRMS (ES^+) $C_{36}H_{43}N_5O_6NaS$ (MNa^+) calcd 696.2832; found 696.2835. $[\alpha]_D$ = −32 (*c* = 1.0, $CHCl_3$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02556.

X-ray crystallographic data (CIF)

Copies of proton and carbon NMR spectra and HPLC traces (PDF)

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Notes

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