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Optically Active N- and C-Terminal Building Blocks for the Synthesis of Peptidyl Olefin Peptidomimetics

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Peptidyl olefin peptidomimetics serve as biologically active compounds or as intermediates for other peptidyl isosteres. The N-terminal side of the C=C bond could be easily prepared in an optically pure form from α-amino acids. Synthesis of C-terminal building blocks in an optically pure form is more challenging. We developed a chemoenzymatic stereoselective approach to such optically active C-terminal building blocks to be assembled into peptidyl olefins by a variety of reactions. They include an electrophilic aldehyde and nucleophilic sulfone, phosphonium salt, phosphonate, and diselenide. Key enzymatic hydrolysis of prochiral diesters to the corresponding hydroxy esters introduces optical activity. The sequence of the subsequent chemical reactions, either protection–hydrolysis–functionalization or functionalization–hydrolysis–protection, determines the absolute stereochemistry of the final building blocks.

Introduction

Peptides function in biological systems as neurotransmitters, hormones, process modulators, toxins, and so on. Peptides are also used as drugs for various diseases (diabetes, growth disorders). However, their pharmaceutical use is limited due to low bioavailability, low metabolic stability, and conformational flexibility that enables binding to several biological targets and, hence, side effects.[1] The potential pharmaceutical applications of peptides on one hand, and their limitations on the other, have led to the development of peptidomimetic analogs. Among these, peptide isosteres containing a replacement of a specific amide bond in the peptide have been extensively used as protease and other enzyme inhibitors. Of special interest among these are peptidyl olefin isosteres, in which a specific peptide bond is replaced by a C=C bond (Figure 1). Peptidyl olefins were used as protease inhibitors,[2] as biologically active compounds,[3] as mechanistic probes,[4] or as intermediates for the synthesis of other peptidyl isosteres such as ethylene-, diol-, epoxide-, and hydroxyethylene-containing peptides (Figure 1).[2b–2d,3h,5]

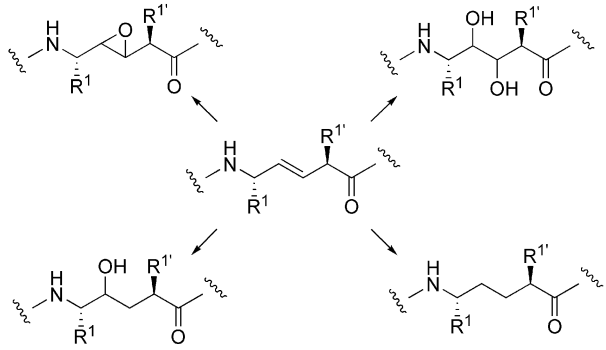

Figure 1. Peptidyl olefins and peptidyl olefin derived peptidyl isosteres.

It is relatively straightforward to control the stereochemistry of the chiral center of the P_1 residue of the peptidyl olefin (the chiral center adjacent to the olefin at its N-terminal side), as it may originate directly from an optically active α-amino acid. The situation is much different at the other side of the double bond (the C-terminal end, or the P_1' residue replacement). The vast majority of the synthetic procedures for peptidyl olefins introduce either a glycine mimetic (= CCH_2CO), which is not chiral, at this position[2a–2d,3c,3d,4a,6] or a substitution (= CCHRCO) in a nonstereoselective manner to produce a diastereomeric mixture of the peptidyl olefin product.[2a–2c,3c–3e,5a–5c,7] Some methods provide optically active products after separation of racemic or diastereomeric intermediates.[8] Only a handful of chiral methods have been introduced, which are based on alkylation in the presence of a chiral auxiliary,[4b] S_N2 organocuprate addition,[3a,3b,3f–3h,9] sigmatropic rearrangement,[10] ring-closing metathesis,[11] and Julia or Wittig reaction between chiral N-terminal nucleophile and C-terminal aldehyde.[2g,12] These methods require long procedures for the preparation of optically pure starting materials, and they provide the products in low overall yields. Thus, efficient stereoselective synthesis of peptidyl olefins still poses a synthetic challenge and an important target. We recently described a new synthetic approach for optically active γ-hydroxy sulfones to serve as C-terminal nucleophilic building blocks for the synthesis of peptidyl ole-

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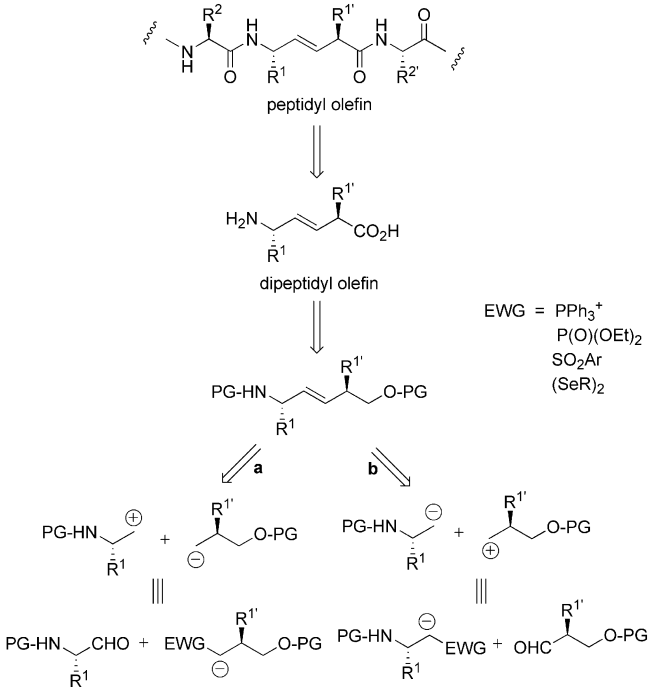
fins.[13] Here we extend our study and describe asymmetric syntheses of both the N-terminal and C-terminal building blocks for the synthesis of peptidyl olefins and other optically active olefins.

Results and Discussion

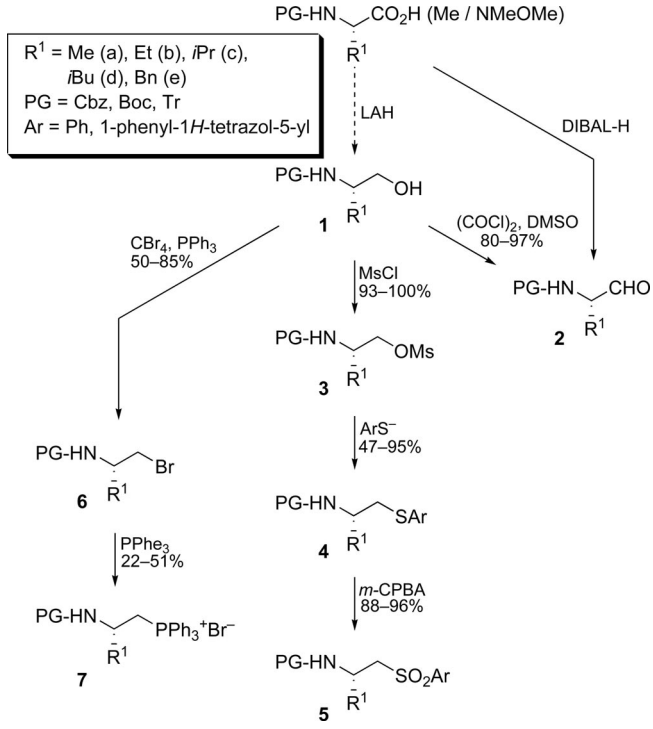
Analysis of the existing methods for the synthesis of peptidyl olefins reveals that most polar reactions between a nucleophile and an electrophile to directly form the new C=C bond are not stereoselective. Most of the chiral methods, on the other hand, are based on a key rearrangement of a pre-existing, sterically well-defined C=C bond. We explored the former, polar approach. We applied standard synthetic protocols for the synthesis of both nucleophilic and electrophilic N-terminal building blocks, utilizing optically active α-amino acids as starting materials. We developed a chemoenzymatic procedure to prepare optically active C-terminal building blocks with various electrophilic and nucleophilic functional groups. These N-terminal and C-terminal compounds could then be condensed into dipeptidyl olefins, followed by peptide extension by standard coupling procedures on both their N-terminal and C-terminal sides according to the desired amino acid sequence. The retrosynthetic analysis of this approach is described in Scheme 1.



Scheme 1. Retrosynthetic analysis for peptidyl olefin peptidomimetics.

The N-Terminal Building Blocks

The synthesis of the various N-terminal (P_1) building blocks starts from optically active α-amino acids or their derivatives (Scheme 2). *N*-Protected α-amino aldehydes **2a**–**e**, derived from the amino acids alanine, ethylglycine, valine, leucine, and phenylalanine, were prepared in high yields either by direct reduction (DIBAL) of the corresponding methyl ester or Weinreb amide or by a reduction (LAH)–oxidation (Swern) sequence. Condensation of nucleophiles with such α-amino aldehydes *N*-protected as carbamates (Cbz or Boc) is hampered by side reactions due to the acidity of the carbamate proton. This problem could be overcome by protection with the trityl protecting group, which keeps the amino proton not acidic.[14] Therefore, we demonstrated the formation of both *N*-Cbz- and *N*-trityl-protected α-amino aldehydes.[14,15]



Scheme 2. The synthesis of N-terminal electrophilic and nucleophilic building blocks.

β-Amino sulfones **5** and β-amino phosphonium salts **7** were synthesized as nucleophilic N-terminal building blocks (Scheme 2). They can interact with C-terminal aldehyde building blocks through the Julia and Wittig reactions, respectively.

Sulfone N-terminal building blocks **5a**–**e**, derived from the α-amino acids alanine, ethylglycine, valine, leucine, and phenylalanine, were prepared according to a published procedure.[12d] They carry either Cbz- or Boc-protecting groups and either thiophenol, for the classical Julia reagent or 1-phenyl-1*H*-tetrazole-5-thiol for the Julia–Kocienski reagent.[16]

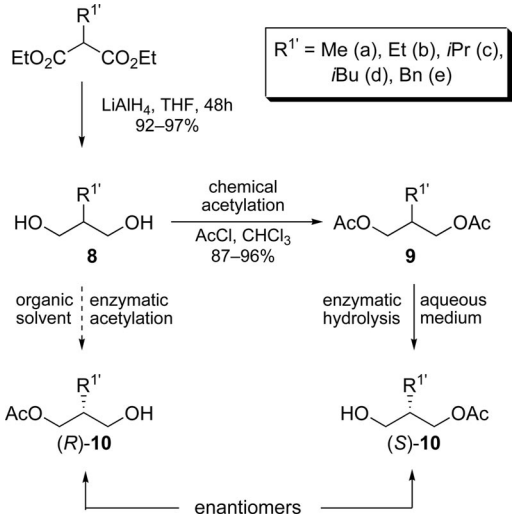
Phosphonium salt building blocks **7a**–**e** were prepared by bromination of α-amino alcohols **1a**–**e**,[17] followed by substitution of the bromide by triphenylphosphane. The modest yields of the latter reactions are due to a competing intramolecular reaction that yields, in addition to the desired phosphonium salt product **7**, also a cyclic carbamate and benzyl bromide. This problem could be overcome by

replacing the *N*-protecting group with trifluoroacetyl.[4a,12a] The carbonyl oxygen of this amide is much less electron rich because of the electron-withdrawing character of the trifluoromethyl substituent, and therefore, it is not nucleophilic enough to compete with the intermolecular nucleophilic reactions.

The C-Terminal Building Blocks

The synthesis of the C-terminal building blocks (both nucleophilic and electrophilic, Scheme 1) is based on a chemoenzymatic protocol that provides a common optically active intermediate, which could then be further chemically manipulated to the various desired compounds.

The key step that provides optical activity in the product is a stereoselective hydrolysis of a prochiral diester, catalyzed by the enzyme lipase. This enzyme can either hydrolyze a prochiral diester to an optically active hydroxy ester in aqueous medium or acylate the corresponding diol to the enantiomeric hydroxy ester in organic solvents (Scheme 3).[18] This approach presents a few advantages: (i) Facile entry to almost any possible substitution by alkylation of diethyl malonate, followed by reduction to the corresponding diol **8** and subsequent diacetylation to **9** (Scheme 3). (ii) Full conversion to the desired optically active product, which stems from the reaction of the enzyme on a homogeneous prochiral compound rather than enzymatic resolution of a racemic mixture. (iii) Control of the stereoselectivity by the mode of the application of the enzyme – either as a hydrolase in aqueous solution or as an acylase in organic solvents. The hydroxy ester product of the enzymatic reaction would then be further manipulated chemically towards the desired C-terminal building blocks.



Scheme 3. Lipase hydrolysis of prochiral diacetates and lipase acetylation of the corresponding prochiral diols produce enantiomeric hydroxy esters.

Synthesis of the Enzyme Substrates

This protocol was applied to five different diethyl malonate compounds substituted with methyl, isopropyl, isobutyl, benzyl, and ethyl groups. When incorporated into peptidyl olefins, these building blocks would mimic the natural amino acids alanine, valine, leucine, and phenylalanine, and the unnatural amino acid ethylglycine, respectively (Scheme 3).[13] Racemic monoacetates were synthesized separately by partial chemical acetylation of the corresponding diols. These compounds were used as references for chiral HPLC analysis of the enzymatic reaction.

The Enzymatic Reaction

We then proceeded to the enzymatic reaction. As discussed above, lipase can act both as a hydrolase in aqueous medium and as an acylase in organic solvents. We studied both directions. Lipases from nine different sources were studied for the acetylation of the five diols **8a**–**e**: from wheat germ, porcine pancreas, *candida rugosa*, *candida cylindracea*, *candida lipolytica*, *rhizopus niveus*, *rhizopus arrhizus*, *pseudomonas cepacia*, and *mucor javanicus*. We examined acetylation by vinyl acetate in chloroform[19] and by acetic anhydride in ether.[20] The best enzyme in our hands was the lipase from *pseudomonas sepacia*, which converted the substrate 2-benzyl-1,3-propanediol (**8e**) into monoacetate product (*R*)-**10e** in only 40–60%*ee*. The other substrates were turned over more slowly and with poorer enantioselectivity.

For the opposite enzymatic reaction, the hydrolysis of diacetyl substrates **9a**–**e** by the *pseudomonas cepacia* lipase under various aqueous conditions was evaluated. The best results in terms of conversion and enantioselectivity were obtained with 40 mM NaCl, 5 mM $CaCl_2$, and 0.07% BSA, with 12.5–40 mg of the enzyme and 100–1000 mg of the substrate. Chiral HPLC analysis identified a single isomer of the products at 50% conversion. The absolute *S* configuration of the products was assigned by comparison to literature data.[18b,21] When carried out further, the hydrolysis of benzyl derivative **9e** at 65% conversion yielded 94%*ee* of desired monoester product **10e**, and hydrolysis of ethyl derivative **9b** at 90% conversion provided product **10b** in 72%*ee*.

Some racemization was observed upon standing of hydroxy ester derivatives **10** in the NMR test tube. This could be explained in terms of migration of the acetyl group between the two prochiral hydroxy groups, through a six-membered ring transition state (Figure 2). This reaction was catalyzed by the very mildly acidic $CDCl_3$ solvent.

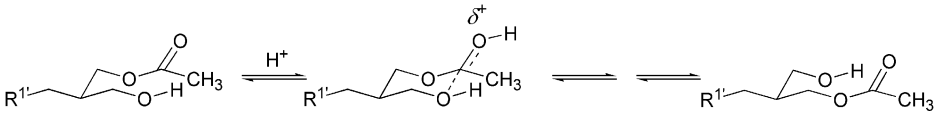
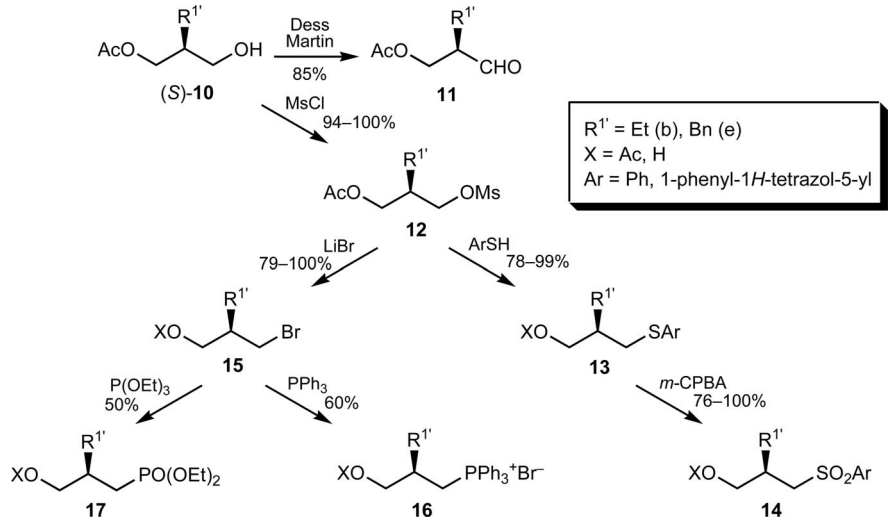


Figure 2. The hydroxy ester racemization mechanism.



Scheme 4. Stereoselective synthesis of C-terminal electrophilic and nucleophilic building blocks of *R* absolute configuration.

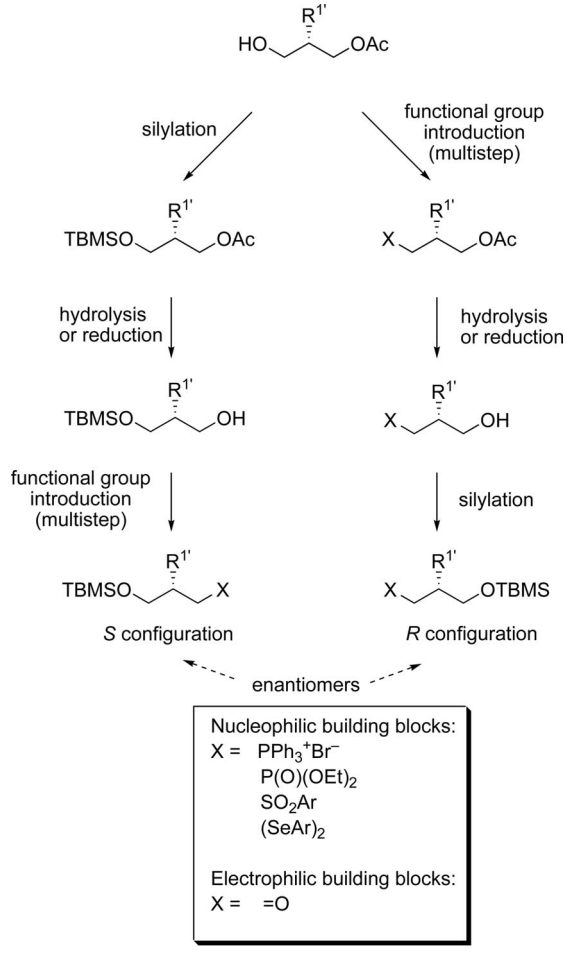
Further Chemical Manipulations to the C-Terminal Building Blocks

Optically active (*S* configuration) hydroxy ester **10** was further chemically modified into one electrophilic and three nucleophilic C-terminal building blocks (Scheme 4). Parallel synthesis with racemic **10** was also carried out to have the necessary standards for chiral HPLC analysis of the stereochemistry of the products. We applied the following protocols to two hydroxy esters **10**: benzyl derivative **10e**, representing the natural amino acid phenylalanine with a large hydrophobic aromatic side chain, and ethyl derivative **10b**, representing the unnatural amino acid ethylglycine with a small aliphatic side chain.

The first C-terminal building block to be synthesized was electrophilic aldehyde **11**. An attempt to apply Swern oxidation to **10e** (the butyryl ester derivative) afforded the elimination product 2-benzyl acrolein. Milder Dess–Martin oxidation afforded desired butyryl ester aldehyde **11e** in good yield and optical purity (95%*ee*).

Three nucleophilic C-terminal building blocks were synthesized, bearing a sulfone (**14**), a phosphonium salt (**16**), or a phosphonate (**17**) as an electron-withdrawing group. These could then be interacted with an N-terminal α-amino aldehyde by the Julia, Wittig, or Emmons–Horner reaction, respectively, to form a precursor of a dipeptidyl olefin.

Sulfone building blocks **14b** and **14e** were prepared by a short and efficient sequence of chemical transformations (Scheme 4).[5e,13] It involved mesylation of hydroxy esters **10** to yield mesylates **12**, substitution with an aromatic thiol to sulfides **13**, and *m*-CPBA oxidation of the latter to the corresponding sulfones **14**. The S_N2 reaction of mesylate **12** with aromatic thiols (either thiophenol or 1-phenyl-1*H*-tetrazole-5-thiol), activated by NaH yielded either ester sulfide **13** (X = Ac) or the corresponding hydroxy sulfide (X = H). The product identity was controlled by the amount of the added base: one equivalent of NaH (relative to the thiol) afforded ester sulfide **13**, whereas two equivalents of the base afforded the corresponding hydroxy sulfide **13′**. Oxidation of sulfides **13** by *m*-CPBA afforded target sulfones **14**.



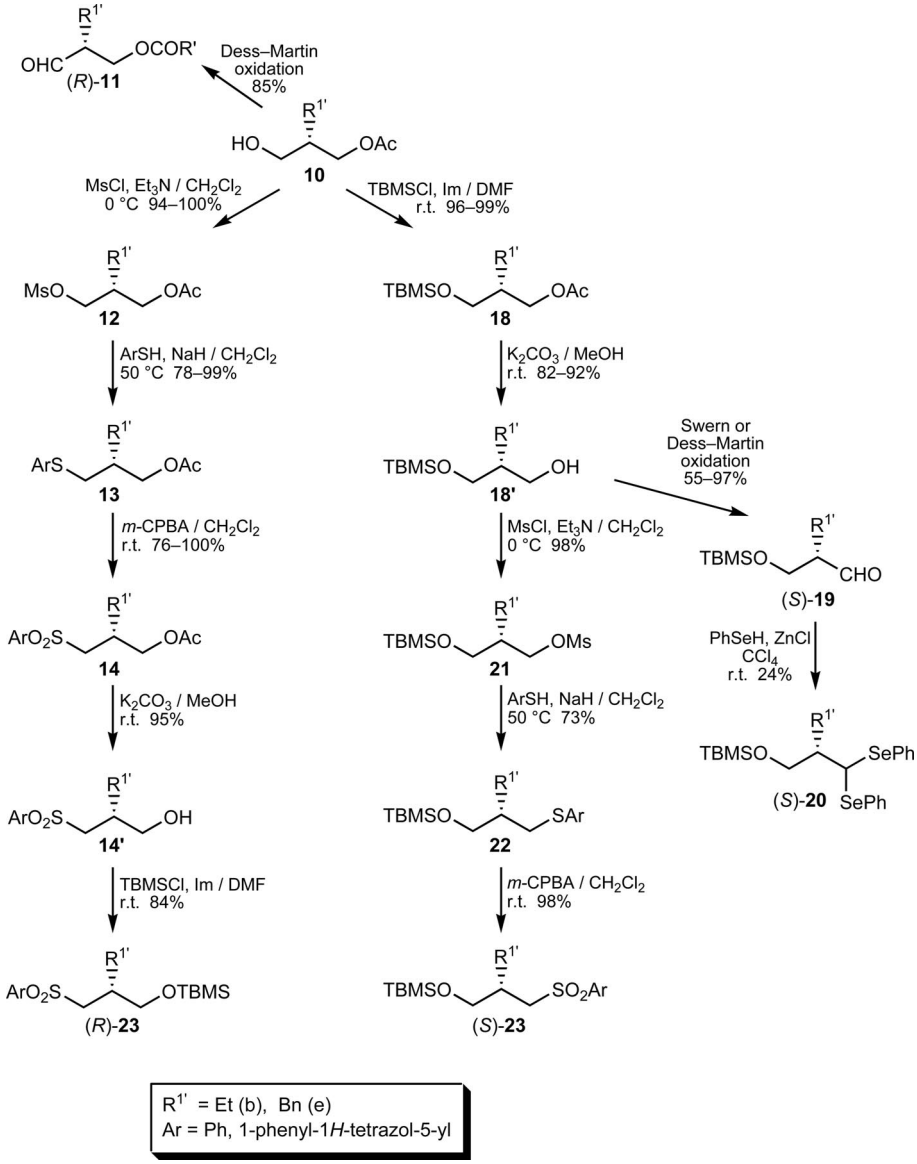
Scheme 5. Stereoselection of final C-terminal building blocks by the sequence of chemical reactions from a common optically active intermediate.

In addition to their application in peptidyl olefin synthesis,[13] optically active β-alkyl-γ-hydroxy sulfones are useful Julia reagents for the synthesis of various natural products and their analogs.[22]

Phosphonium salt (Wittig reagent) C-terminal building blocks could also be prepared from mesylates **12** (Scheme 4).[18c] Attempts to transform the mesylates directly into phosphonium salts **16** failed. Therefore, they were first transformed into bromides **15**. The acetoxy group of bromides **15** was reduced by DIBAL-H to hydroxy bromides **15′**, followed by displacement of the bromide by triphenylphosphane to afford the desired Wittig reagent building blocks **16′**. Such phosphonium salts were previously used in the synthesis of natural products.[18c,22l,23] Bromide **15e** also underwent Arbuzov reaction with triethyl phosphite to yield the corresponding phosphonate **17e**.

All of the benzyl derivatives along the various synthetic routes were analyzed by chiral HPLC for their optical purity (in comparison with the corresponding racemic mixtures). The results demonstrated at least 90% retention of steric integrity in all of the synthetic transformations.

The enzymatic hydrolytic reaction determined the absolute stereochemistry of its hydroxy ester product **10**. Enzymatic acetylation in organic medium would yield the enantiomeric hydroxy ester, but the latter did not proceed in satisfactory enantioselectivity. Alternatively, the order of further chemical manipulations could provide a second opportunity to control the stereochemistry of the final C-terminal building blocks. Thus, as shown in Scheme 4, transformation of the original free hydroxy group into the desired electrophilic and nucleophilic functional groups yielded the *R* enantiomer of the aldehyde, sulfone, phosphonium salt, and phosphonate building blocks. On the other hand, protection (silylation) of the free hydroxy group of **10**, followed by acetyl hydrolysis and transformation of the new free hydroxy group into the desired electrophilic and nucleophilic



Scheme 6. Stereoselective synthesis of the two enantiomers of the C-terminal building blocks. Aldehyde (*R*)-**11e** was prepared from the corresponding butyryl ester.

functional groups would provide the *S* enantiomer of the final products (Scheme 5). This was demonstrated in the stereoselective preparation of the *S* enantiomer of one electrophilic (aldehyde) and two nucleophilic (sulfone and diselenide) C-terminal building blocks of both the benzyl and the ethyl derivatives.

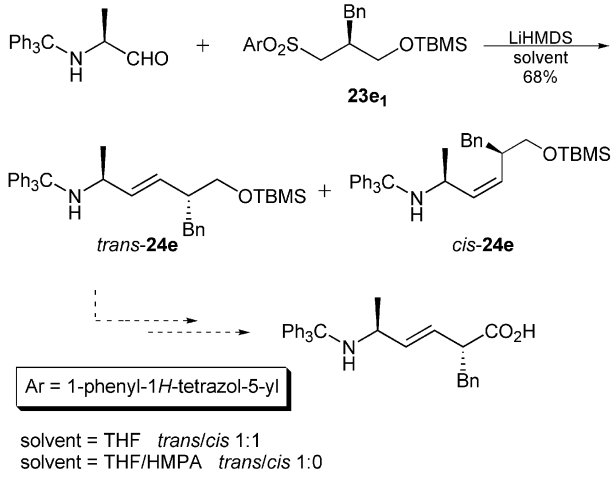
We demonstrated above the direct oxidation of hydroxy ester **10e** to the corresponding *R* ester aldehyde **11e**. Alternatively, hydroxy esters **10b** and **10e** were silylated (**18**), followed by ester hydrolysis under mild basic conditions (**18′**), and oxidation of the newly exposed alcohols under either Swern or Dess–Martin conditions provided the corresponding *S* aldehydes **19** (Scheme 6). Thus, aldehydes of both *R* and *S* configuration were prepared in high optical purity from the same enzymatic product **10**.

Aldehyde (*S*)-**19e** was further transformed into new nucleophilic C-terminal building block diselenide **20e** (Scheme 6).[24] This transformation demonstrates the simplicity of the approach in controlling the absolute configuration of a C-terminal nucleophilic building block by the order of the chemical transformations from single isomer starting material **10**.

We further applied the control of product stereochemistry by modification of the sequence of chemical reactions from optically active hydroxy ester **10**, either functionalization–hydrolysis–protection or protection–hydrolysis–functionalization (Scheme 5), to the synthesis of the two stereoisomers of sulfone C-terminal building blocks (Scheme 6). We described above the synthesis of the *R* enantiomer of sulfone compounds **14** on the basis of the functionalization-first sequence (Scheme 6, left branch). Sulfone **14′e** was also silylated to give the *R* enantiomer of protected sulfone **23e**. Alternatively, benzyl hydroxy ester **10e** was silylated on the free hydroxy group in quantitative yield, providing orthogonally doubly protected diol **18e**. Selective hydrolysis to acetate **18′e**, followed by the short set of functionalization reactions used above (mesylation to **21e**, formation of sulfide **22e$_1$**, and oxidation) afforded the *S* enantiomer of sulfone **23e$_1$** (subscript "1" denotes the 1-phenyl-1*H*-tetrazol-5-yl derivatives).

Peptidyl Olefins

To demonstrate the utility of the C-terminal building blocks, we used two such units, with different side chains (ethyl and benzyl) and two opposite stereoisomers (*R* and *S*, respectively) for the synthesis of peptidyl olefin precursors. We treated the lithium salt of *S* sulfone **23e$_1$** with *N*-tritylalaninal[14] in THF (Julia–Kocienski reaction, Scheme 7).[25] The desired product (2*R*,5*S*)-2-benzyl-1-(*tert*-butyldimethylsilyloxy)-5-tritylamino-hex-3-ene (**24e**), the olefin isoster of *N*-trityl-alanylphenylalaninol, was obtained as a 1:1 mixture of *E*/*Z* isomers (which were separated by chromatography) in 68% yield. No racemization at the chiral centers was detected. The product could then be transformed into the dipeptidyl olefin by alcohol deprotection and oxidation, as previously demonstrated.[3f,5c,7b] When the same Julia–Kocienski reaction was carried out in a more polar solvent, namely, 10% HMPA in THF, only the *trans* isomer of olefin **24e** was obtained as a pure single diastereomer, though at a lower 31% yield.[18c] Similarly, the pure *trans* isomer (2*S*,5*S*)-1-(*tert*-butyldimethylsilyloxy)-2-ethyl-5-tritylamino-hex-3-ene (**24b**) was obtained in 22% yield from *R* sulfone **23b$_1$** and *N*-tritylalaninal. Further studies for the optimization of this reaction are currently in progress.



Scheme 7. The Julia–Kocienski reaction of C-terminal (P_1') sulfone building blocks towards dipeptidyl olefins.

Conclusions

In this study we developed a new efficient approach for the preparation of optically active nucleophilic and electrophilic C-terminal (P_1') building blocks for the synthesis of peptidyl olefin peptidomimetics. The nucleophilic functional groups include sulfones, phosphonium salts, phosphonates, and diselenides. Aldehydes serve as the electrophilic group. This approach is based on a key enzymatic reaction: stereoselective hydrolysis of prochiral diesters to optically active hydroxy esters. The role of the enzymatic reaction is only to provide high optical purity, rather than to define the stereochemistry of the final C-terminal building block products. The absolute configuration is eventually determined by the sequence of the subsequent chemical reactions towards the final building block: either protection–hydrolysis–functionalization (yielding the *S* configuration) or functionalization–hydrolysis–protection (yielding the *R* configuration). A set of electrophilic (aldehyde) and nucleophilic (sulfone, phosphonium salts, and phosphonate) N-terminal building blocks complements the C-terminal building blocks for the synthesis of peptidyl olefins peptidomimetics. We demonstrated formation of two precursors of dipeptidyl olefin isosteres in pure enantiomeric form by the Julia–Kocienski reaction between optically active C-terminal sulfones and an N-terminal α-amino aldehyde.

Experimental Section

General: Anhydrous solvents were dried and freshly distilled (THF, DME, ether, and toluene from sodium/benzophenone, DMF from molecular sieves, and CH_2Cl_2 from $CaCl_2$). Chromatography refers to flash column chromatography carried out on silica gel 60 (230–400 mesh ASTM, E. Merck) by using analytical-grade solvents. TLC was performed on E. Merck 0.2 mm percolated silica gel F-254 plates. Compounds were detected by UV light (254 nm) and/or by staining with vanillin, Cl_2/KI-tolidine,[26] or phosphomolybdic acid. ^1H and ^{13}C NMR spectra were recorded at 600 or 300 MHz and 150 or 75 MHz, respectively, in $CDCl_3$, unless otherwise indicated. Chemical shifts are reported in ppm relative to TMS in $CDCl_3$ or relative to solvent resonance in other solvents. Most ^1H NMR assignments were supported by 2D homonuclear COSY experiments. ^{13}C NMR assignments were supported by DEPT or 2D heteronuclear COSY (HMQC) and heteronuclear multiple bond connectivity (HMBC) experiments. Mass spectra were recorded in DCI mode with methane as the reagent gas. HPLC was carried out on CHIRALCEL$_R$ OD-H 250 × 10 mm or CHIRA GROM 250x2 mm chiral columns, at flow rates of 1 and 0.3 mL min^{-1}, respectively.

Synthesis of N-Terminal Building Blocks

Cbz-α-Amino Aldehydes (2): A solution of DMSO (0.83 mL, 11.7 mmol) in dry CH_2Cl_2 (3 mL) was added to a stirred solution of oxalyl chloride (0.46 mL, 5.26 mmol) in dry CH_2Cl_2 (13 mL), under an argon atmosphere at –60 °C. After 10 min, a solution of Cbz-amino alcohol (4.8 mmol) in dry CH_2Cl_2 (7 mL) was added, and the reaction mixture was stirred for 15 min at –60 °C. Et_3N (3.3 mL, 23.9 mmol) was added, and the cooling bath was removed, allowing the solution to reach room temperature. The mixture was stirred for an additional 20 min. Water was added, and the aqueous phase was re-extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed successively with water, 0.5 M HCl solution (2×), water, and saturated NaCl solution. The organic layer was dried with $MgSO_4$, filtered, and concentrated. Purification by chromatography (hexane/EtOAc, 3:1) afforded the clean aldehyde as a yellow oil.

Cbz-Alaninal (2a): Yield: 670 mg, 67%. ^1H NMR: δ = 9.48 (s, 1 H), 7.34–7.25 (m, 5 H), 5.70 (br. d, 1 H), 5.09 (s, 2 H), 4.23 (quint., J = 7.2 Hz, 1 H), 1.29 (d, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 199.5, 156.0, 136.1, 128.5, 128.2, 128.1, 67.0, 55.8, 14.5 ppm. MS: m/z (%) = 208 (12) $[M + H]^+$, 178 (18), 91 (100). HRMS: calcd. for $C_{11}H_{14}NO_3$ $[M + H]^+$ 208.0974; found 208.0989.

Cbz-Ethylglycinal (2b): Yield: 1.01 g, 95%. ^1H NMR: δ = 9.56 (s, 1 H), 7.37–7.31 (m, 5 H), 5.44 (br. d, 1 H), 5.12 (s, 1 H), 4.28 (q, J = 6.6 Hz, 1 H), 1.97 (dqd, J = 14.4, 7.5, 5.7 Hz, 1 H), 1.69 (dquint., J = 14.4, 7.2, Hz, 1 H), 0.95 (t, J = 7.5, Hz, 3 H) ppm. ^{13}C NMR: δ = 199.4, 156.2, 136.3, 128.7, 128.3, 128.2, 67.2, 61.3, 22.4, 9.4 ppm. MS: m/z (%) = 222 (4) $[M + H]^+$, 192 (27), 148 (20), 91 (100). HRMS: calcd. for $C_{12}H_{16}NO_3$ $[M + H]^+$ 222.1130; found 222.1108.

Cbz-Valinal (2c): Yield: 1.09 g, 96%. ^1H NMR: δ = 9.38 (s, 1 H), 7.18–7.09 (m, 5 H), 5.78 (d, J = 8.1 Hz, 1 H), 4.94 (s, 2 H), 4.10 (dd, J = 8.1, 4.5 Hz, 1 H), 2.07 (dsept., J = 6.9, 4.5 Hz, 1 H), 0.84 (d, J = 6.9 Hz, 3 H), 0.74 (dd, J = 6.9, 0.6 Hz, 3 H) ppm. ^{13}C NMR: δ = 200.0, 156.3, 136.1, 128.2, 127.8, 127.7, 66.6, 64.8, 28.5, 18.7, 17.2 ppm. MS: m/z (%) = 236 (10) $[M + H]^+$, 206 (21), 162 (32), 91 (100). HRMS: calcd. for $C_{13}H_{18}NO_3$ $[M + H]^+$ 236.1287; found 236.1256.

Cbz-Leucinal (2d): Yield: 1.17 g, 97%. ^1H NMR: δ = 9.52 (s, 1 H), 7.36–7.25 (m, 5 H), 5.53 (br. d, 1 H), 5.09 (s, 2 H), 4.27 (td, J = 8.3, 4.2 Hz, 1 H), 1.73 (non., J = 6.3 Hz, 1 H), 1.63 (ddd, J = 14.1, 8.7, 5.1 Hz, 1 H), 1.38 (ddd, J = 14.1, 9.3, 5.1 Hz, 1 H), 0.95 (d, J = 6.3 Hz, 3 H), 0.93 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR: δ = 200.1, 156.3, 136.2, 128.5, 128.2, 128.0, 67.0, 58.8, 37.8, 24.5, 23.0, 21.8 ppm. MS: m/z (%) = 250 (4) $[M + H]^+$, 220 (13), 176 (14), 91 (100). HRMS: calcd. for $C_{14}H_{20}NO_3$ $[M + H]^+$ 250.1443; found 250.1437.

Cbz-Phenylalaninal (2e): Yield: 1.09 g, 80%. ^1H NMR: δ = 9.57 (s, 1 H), 7.37–7.09 (m, 10 H), 5.40 (d, J = 6.6 Hz, 1 H), 5.07 (s, 2 H), 4.46 (q, J = 6.7 Hz, 1 H), 3.12 (dd, J = 13.8, 6.8 Hz, 1 H), 3.05 (dd, J = 13.8, 6.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 199.0, 156.0, 136.2, 135.5, 129.3, 128.8, 128.6, 128.3, 128.2, 127.2, 67.1, 61.1, 35.3 ppm. MS: m/z (%) = 284 (4) $[M + H]^+$, 254 (13), 210 (15), 91 (100). HRMS: calcd. for $C_{17}H_{18}NO_3$ $[M + H]^+$ 284.1287; found 284.1276.

The syntheses of trityl-alaninal (**2′a**), trityl-leucinal (**2′d**), and trityl-phenylalaninal (**2′e**) were described previously.[14]

Methanesulfonates 3: Prepared from the corresponding alcohols **1** according to a published procedure.[12d]

Cbz-Alaninol Methanesulfonate (3a): Yield: 93%. ^1H NMR: δ = 7.34–7.33 (m, 5 H), 5.09 (obscured, 1 H), 5.09 (s, 2 H), 4.22 (dd, J = 10.1, 4.5 Hz, 1 H), 4.13 (dd, J = 9.9, 4.5 Hz, 1 H), 4.02 (m, 1 H), 2.94 (s, 3 H), 1.22 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR: δ = 155.7, 136.3, 128.6, 128.3, 128.2, 71.8, 66.9, 46.1, 37.2, 10.1 ppm. MS: m/z (%) = 287 $[M]^+$, 178 (7), 108 (30), 91 (100). HRMS: calcd. for $C_{12}H_{18}NO_5S$ $[M + H]^+$ 288.0906; found 288.0905.

Cbz-Ethylglycinol Methanesulfonate (3b): Yield: 100%. ^1H NMR: δ = 7.33–7.27 (m, 5 H), 5.30 (d, J = 8.4 Hz, 1 H), 5.10 (d, J = 11.4 Hz, 1 H), 5.06 (d, J = 11.4 Hz, 1 H), 4.21 (dd, J = 10.2, 4.2 Hz, 1 H), 4.15 (dd, J = 10.2, 4.5 Hz, 1 H), 3.79 (tdt, J = 8.4, 6.3, 4.4 Hz, 1 H), 2.90 (s, 3 H), 1.57 (dqd, J = 13.5, 7.3, 6.3 Hz, 1 H), 1.51 (ddq, J = 13.5, 8.4, 7.3 Hz, 1 H), 0.94 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR: δ = 156.0, 136.3, 128.4, 128.1, 127.9, 70.6, 66.6, 51.6, 37.0, 24.0, 10.2 ppm. MS: m/z (%) = 302 (93) $[M + H]^+$, 258 (60), 206 (65), 192 (99), 108 (80), 92 (97), 79 (32). HRMS: calcd. for $C_{13}H_{20}NO_5S$ $[M + H]^+$ 302.1062; found 302.1065.

Cbz-Valinol Methanesulfonate (3c): ^1H NMR: δ = 7.35–7.30 (m, 5 H), 5.12 (obscured, 1 H), 5.12 (d, J = 12.3 Hz, 1 H), 5.08 (d, J = 12.3 Hz, 1 H), 4.25 (d, J = 4.5 Hz, 2 H), 3.70 (ddt, J = 9.3, 6.9, 4.5 Hz, 1 H), 2.93 (s, 3 H), 1.87 (oct., J = 6.8 Hz, 1 H), 0.97 (d, J = 6.9 Hz, 3 H), 0.95 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR: δ = 156.2, 136.4, 128.6, 128.2, 128.1, 69.5, 66.9, 55.6, 37.2, 29.1, 19.3, 18.5 ppm. MS: m/z (%) = 316 (9) $[M + H]^+$, 206 (31), 181 (12), 108 (58), 91 (100). HRMS: calcd. for $C_{14}H_{22}NO_5S$ $[M + H]^+$ 316.1219; found 316.1208.

Cbz-Leucinol Methanesulfonate (3d): ^1H NMR: δ = 7.38–7.27 (m, 5 H), 5.01 (d, J = 12.2 Hz, 1 H), 4.97 (d, J = 12.2 Hz, 1 H), 4.94 (d, J = 8.4 Hz, 1 H), 4.15 (dd, J = 10.2, 3.9 Hz, 1 H), 4.03 (dd, J = 10.2, 4.5 Hz, 1 H), 3.88 (tq, J = 9.2, 4.6 Hz, 1 H), 2.93 (s, 3 H), 1.57 (doct., J = 8.7, 6.5 Hz, 1 H), 1.35 (ddd, J = 14.1, 9.6, 5.7 Hz, 1 H), 1.23 (ddd, J = 14.1, 8.7, 5.4 Hz, 1 H), 0.93 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR: δ = 155.9, 136.4, 128.6, 128.2, 128.1, 71.4, 66.9, 48.5, 39.9, 37.2, 24.6, 23.0, 21.9 ppm. MS: m/z (%) = 329 (9) $[M]^+$, 220 (12), 176 (22), 108 (17), 91 (100). HRMS: calcd. for $C_{15}H_{23}NO_5S$ $[M]^+$ 329.1297; found 329.1293.

Cbz-Phenylalaninol Methanesulfonate (3e): ^1H NMR: δ = 7.32–7.20 (m, 10 H), 5.25 (d, J = 8.1 Hz, 1 H), 5.05 (s, 2 H), 4.22 (dd, J = 9.3, 3.3 Hz, 1 H), 4.15 (qt, J = 7.5, 3.7 Hz, 1 H), 4.09 (dd, J = 9.3, 3.9 Hz, 1 H), 2.90 (s, 3 H), 2.89 (dd, J = 13.8, 7.2 Hz, 1 H), 2.84 (dd, J = 13.8, 7.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 155.8, 136.5, 136.3, 129.2, 128.8, 128.6, 128.2, 128.1, 127.0, 69.7, 66.8, 51.4, 37.1,

37.0 ppm. MS: *m*/*z* (%) = 364 (1) $[M + H]^+$, 272 (17), 228 (17), 176 (7), 132 (6), 91 (100). HRMS: calcd. for $C_{18}H_{22}NO_5S$ $[M + H]^+$ 364.1219; found 364.1203.

Sulfides 4: Prepared from the corresponding methanesulfonates **3** according to a published procedure.[12d]

(*N*-Cbz-2-amino)propyl Phenyl Sulfide (4a): ^{1}H NMR: δ = 7.35–7.11 (m, 10 H), 5.07 (d, *J* = 12.3 Hz, 1 H), 5.03 (d, *J* = 12.3 Hz, 1 H), 5.03 (obscured, 1 H), 3.94 (m, 1 H), 3.12 (dd, *J* = 13.5, 5.1 Hz, 1 H), 2.93 (dd, *J* = 13.5, 6.0 Hz, 1 H), 1.20 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR: δ = 155.6, 136.5, 136.0, 129.4, 129.0, 128.5, 128.1, 128.1, 126.2, 66.6, 46.7, 40.1, 19.8 ppm. MS: *m*/*z* (%) = 301 (100) $[M]^+$, 192 (15), 178 (7), 150 (20), 124 (23), 91 (60). HRMS: calcd. for $C_{17}H_{19}NO_2S$ $[M]^+$ 301.1137; found 301.1095.

(*N*-Cbz-2-amino)butyl Phenyl Sulfide (4b): ^{1}H NMR: δ = 7.35–7.13 (m, 10 H), 5.07 (d, *J* = 12.6 Hz, 1 H), 5.03 (d, *J* = 12.6 Hz, 1 H), 4.99 (d, *J* = 9.6 Hz, 1 H), 3.78 (ddq, *J* = 9.6, 7.5, 5.6 Hz, 1 H), 3.09 (dd, *J* = 13.5, 5.7 Hz, 1 H), 3.01 (dd, *J* = 13.5, 5.7 Hz, 1 H), 1.66 (dqd, *J* = 14.1, 7.5, 5.4 Hz, 1 H), 1.46 (dquint., *J* = 14.1, 7.5 Hz, 1 H), 0.88 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 156.0, 136.5, 136.3, 129.4, 129.0, 128.5, 128.0, 128.0, 126.2, 66.6, 52.3, 38.6, 26.6, 10.3 ppm. MS: *m*/*z* (%) = 315 (26) $[M]^+$, 192 (25), 164 (23), 124 (32), 91 (100). HRMS: calcd. for $C_{18}H_{21}NO_2S$ $[M]^+$ 315.1293; found 315.1311.

(*N*-Cbz-2-amino)-3-methylbutyl Phenyl Sulfide (4c): ^{1}H NMR: δ = 7.35–7.10 (m, 10 H), 5.06 (s, 2 H), 5.01 (d, *J* = 9.3 Hz, 1 H), 3.72 (dq, *J* = 9.0, 6.2 Hz, 1 H), 3.02 (d, *J* = 6.0 Hz, 2 H), 1.90 (oct., *J* = 6.8 Hz, 1 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 0.86 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR: δ = 156.2, 136.6, 136.2, 129.6, 128.9, 128.4, 126.0, 126.2, 66.6, 55.8, 37.2, 30.8, 19.4, 17.7 ppm. MS: *m*/*z* (%) = 329 (41) $[M]^+$, 220 (9), 206 (43), 178 (21), 123 (28), 91 (50). HRMS: calcd. for $C_{19}H_{23}NO_2S$ $[M]^+$ 329.1450; found 329.1446.

(*N*-Cbz-2-amino)-4-methylpentyl Phenyl Sulfide (4d): ^{1}H NMR: δ = 7.38–7.14 (m, 10 H), 5.05 (s, 2 H), 4.89 (d, *J* = 7.8 Hz, 1 H), 3.95 (tq, *J* = 8.0, 5.4 Hz, 1 H), 3.10 (dd, *J* = 13.4, 5.1 Hz, 1 H), 3.04 (dd, *J* = 13.4, 5.7 Hz, 1 H), 1.61 (non., *J* = 6.6 Hz, 1 H), 1.44 (ddd, *J* = 13.7, 8.1, 5.1 Hz, 1 H), 1.37 (ddd, *J* = 13.7, 8.7, 6.0 Hz, 1 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR: δ = 155.8, 136.5, 136.4, 129.6, 129.0, 128.5, 128.1, 128.1, 126.2, 66.7, 49.1, 42.9, 39.6, 24.9, 23.1, 22.1 ppm. MS: *m*/*z* (%) = 344 (36) $[M + H]^+$, 343 (51) $[M]^+$, 234 (21), 220 (44), 192 (15), 176 (71), 124 (29), 91 (100). HRMS: calcd. for $C_{20}H_{26}NO_2S$ $[M + H]^+$ 344.1684; found 344.1699.

(*N*-Cbz-2-amino)-3-phenylpropyl Phenyl Sulfide (4e): ^{1}H NMR: δ = 7.33–7.08 (m, 15 H), 5.04 (d, *J* = 12.8 Hz, 1 H), 5.01 (d, *J* = 12.8 Hz, 1 H), 4.94 (d, *J* = 7.8 Hz, 1 H), 4.10 (sext., *J* = 6.5 Hz, 1 H), 3.04 (d, *J* = 5.4 Hz, 2 H), 2.92 (d, *J* = 6.6 Hz, 2 H) ppm. ^{13}C NMR: δ = 155.7, 137.3, 136.5, 135.9, 129.7, 129.46, 129.1, 128.7, 128.6, 128.2, 128.1, 126.8, 126.4, 66.7, 51.9, 39.3, 37.6 ppm. MS: *m*/*z* (%) = 377 (1) $[M]^+$, 135 (100), 133 (96). HRMS: calcd. for $C_{23}H_{23}NO_2S$ $[M]^+$ 377.1450; found 377.1423.

(*N*-Cbz-2-amino)butyl (1-Phenyl-1*H*-tetrazole-5-yl) Sulfide ($4b_1$): ^{1}H NMR: δ = 7.51 (s, 5 H), 7.27 (s, 5 H), 5.31 (d, *J* = 8.7 Hz, 1 H), 5.03 (s, 2 H), 3.95 (dquint., *J* = 7.8, 4.2 Hz, 1 H), 3.64 (dd, *J* = 13.5, 4.2 Hz, 1 H), 3.47 (dd, *J* = 13.8, 8.7 Hz, 1 H), 1.67 (dquint., *J* = 14.1, 7.0 Hz, 1 H), 1.58 (dquint., *J* = 14.1, 7.4 Hz, 1 H), 0.96 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 156.2, 154.5, 136.5, 133.5, 130.2, 129.8, 128.5, 128.0, 127.8, 123.9, 66.6, 52.6, 37.8, 27.5, 10.4 ppm. MS: *m*/*z* (%) = 384 (21) $[M + H]^+$, 276 (7), 192 (8), 148 (14), 118 (15), 91 (100). HRMS: calcd. for $C_{19}H_{22}N_5O_2S$ $[M + H]^+$ 384.1494; found 384.1460.

Sulfones 5: Prepared from the corresponding sulfides **4** according to a published procedure.[12d]

(*N*-Cbz-2-amino)propyl Phenyl Sulfone (5a): Yield: 84% (overall from **1a**). ^{1}H NMR: δ = 7.86 (d, *J* = 7.8 Hz, 2 H), 7.55 (tt, *J* = 7.5, 1.4 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 2 H), 7.31–7.25 (m, 5 H), 5.61 (d, *J* = 7.2 Hz, 1 H), 4.97 (s, 2 H), 4.09 (dqdd, *J* = 7.2, 6.9, 6.6, 4.8 Hz, 1 H), 3.47 (dd, *J* = 13.8, 6.6 Hz, 1 H), 3.15 (dd, *J* = 14.1, 4.8 Hz, 1 H), 1.27 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR: δ = 155.1, 139.4, 136.2, 133.6, 129.1, 128.3, 127.9, 127.8, 127.7, 66.3, 60.2, 43.2, 20.5 ppm. MS: *m*/*z* (%) = 334 (64) $[M + H]^+$, 290 (93), 226 (12), 108 (34), 91 (100). HRMS: calcd. for $C_{17}H_{20}NO_4S$ $[M + H]^+$ 334.1113; found 334.1110.

(*N*-Cbz-2-amino)butyl Phenyl Sulfone (5b): Yield: 77% (overall from **1b**). ^{1}H NMR: δ = 7.88 (d, *J* = 7.5 Hz, 2 H), 7.59 (tt, *J* = 7.4, 1.2 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 2 H), 7.37–7.26 (m, 5 H), 5.30 (d, *J* = 8.1 Hz, 1 H), 5.01 (d, *J* = 12.6 Hz, 1 H), 4.98 (d, *J* = 12.6 Hz, 1 H), 3.92 (dquint., *J* = 7.5, 4.8 Hz, 1 H), 3.47 (dd, *J* = 14.4, 7.5 Hz, 1 H), 3.23 (dd, *J* = 14.4, 4.2 Hz, 1 H), 1.71 (dqd, *J* = 13.5, 7.5, 6.0 Hz, 1 H), 1.66 (dquint., *J* = 13.5, 7.5 Hz, 1 H), 0.88 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 155.6, 139.7, 136.4, 133.8, 129.3, 128.5, 128.1, 128.0, 127.9, 66.6, 59.0, 49.1, 27.4, 10.2 ppm. MS: *m*/*z* (%) = 348 (36) $[M + H]^+$, 304 (21), 240 (13), 108 (100), 91 (64). HRMS: calcd. for $C_{18}H_{22}NO_4S$ $[M + H]^+$ 348.1270; found 348.1262.

(*N*-Cbz-2-amino)butyl (1-phenyl-1*H*-tetrazole-5-yl) Sulfone ($5b_1$): Yield: 53% (overall from **1b**). ^{1}H NMR: δ = 7.66–7.52 (m, 5 H), 7.36–7.26 (m, 5 H), 5.14 (br. s, 1 H), 4.99 (s, 2 H), 4.18 (m, 1 H), 4.02 (dd, *J* = 15.0, 7.8 Hz, 1 H), 3.88 (dd, *J* = 15.0, 4.2 Hz, 1 H), 1.74 (quint., *J* = 6.5 Hz, 2 H), 0.96 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 155.6, 153.9, 136.2, 133.1, 131.6, 129.7, 128.6, 128.3, 128.1, 125.5, 67.0, 59.4, 48.7, 27.7, 10.3 ppm. MS: *m*/*z* (%) = 416 (5) $[M + H]^+$, 308 (11), 147 (14), 108 (14), 91 (100). HRMS: calcd. for $C_{19}H_{22}N_5O_4S$ $[M + H]^+$ 416.1393; found 416.1348.

(*N*-Cbz-2-amino)-3-methylbutyl Phenyl Sulfone (5c): Yield: 43% (overall from **1c**). ^{1}H NMR: δ = 7.89 (d, *J* = 7.5 Hz, 2 H), 7.59 (tt, *J* = 7.5, 1.2 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 2 H), 7.39–7.28 (m, 5 H), 5.14 (d, *J* = 8.7 Hz, 1 H), 5.03 (d, *J* = 12.5 Hz, 1 H), 5.00 (d, *J* = 12.5 Hz, 1 H), 3.88 (tdd, *J* = 8.7, 6.5, 3.3 Hz, 1 H), 3.38 (dd, *J* = 14.7, 8.6 Hz, 1 H), 3.24 (dd, *J* = 14.7, 3.3 Hz, 1 H), 2.01 (oct., *J* = 6.6 Hz, 1 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR: δ = 155.7, 139.2, 136.4, 133.6, 129.1, 128.3, 127.9, 127.8, 66.4, 57.3, 52.1, 32.1, 18.6, 17.6 ppm. MS: *m*/*z* (%) = 362 (55) $[M + H]^+$, 319 (24), 254 (68), 108 (100). HRMS: calcd. for $C_{19}H_{24}NO_4S$ $[M + H]^+$ 362.1426; found 362.1422.

(*N*-Cbz-2-amino)-4-methylpentyl Phenyl Sulfone (5d): Yield: 68% (overall from **1d**). ^{1}H NMR: δ = 7.89 (d, *J* = 7.5 Hz, 2 H), 7.60 (tt, *J* = 7.5, 1.2 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 2 H), 7.38–7.28 (m, 5 H), 5.23 (d, *J* = 8.4 Hz, 1 H), 5.02 (d, *J* = 12.2 Hz, 1 H), 4.97 (d, *J* = 12.2 Hz, 1 H), 4.05 (tdt, *J* = 9.1, 6.9, 4.8 Hz, 1 H), 3.48 (dd, *J* = 14.5, 6.8 Hz, 1 H), 3.24 (dd, *J* = 14.5, 4.4 Hz, 1 H), 1.61 (non., *J* = 6.0 Hz, 1 H), 1.52 (ddd, *J* = 15.0, 8.7, 4.6 Hz, 1 H), 1.46 (ddd, *J* = 15.0, 9.9, 7.8 Hz, 1 H), 0.85 (d, *J* = 6.0 Hz, 6 H) ppm. ^{13}C NMR: δ = 155.5, 139.9, 136.4, 133.8, 129.3, 128.6, 128.2, 128.0, 127.9, 66.7, 59.6, 46.1, 43.2, 24.8, 22.8, 21.8 ppm. MS: *m*/*z* = 376 $[M + H]^+$, 332, 240, 91. HRMS (MALDI-TOF): calcd. for $C_{20}H_{26}NO_4S$ $[M + H]^+$ 376.1577; found 376.1587.

(*N*-Cbz-2-amino)-3-phenylpropyl Phenyl Sulfone (5e): Yield: 44% (overall from **1e**). ^{1}H NMR: δ = 7.87 (d, *J* = 7.5 Hz, 2 H), 7.63 (tt, *J* = 7.5, 1.2 Hz, 1 H), 7.51 (t, *J* = 7.5 Hz, 2 H), 7.42–7.12 (m, 10 H), 5.19 (d, *J* = 6.9 Hz, 1 H), 5.05 (d, *J* = 12.2 Hz, 1 H), 4.98 (d, *J* = 12.2 Hz, 1 H), 4.21 (dquint., *J* = 7.2, 4.8 Hz, 1 H), 3.49 (dd, *J*

= 14.4, 7.8 Hz, 1 H), 3.29 (dd, *J* = 14.4, 4.8 Hz, 1 H), 3.09 (dd, *J* = 13.8, 6.9 Hz, 1 H), 3.02 (dd, *J* = 13.8, 7.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 155.4, 139.7, 136.3, 136.4, 133.9, 129.5, 129.4, 128.9, 128.6, 128.3, 128.2, 128.0, 127.1, 66.8, 57.9, 49.2, 39.9 ppm. MS (ESI): *m*/*z* = 432 (100) $[M + Na]^+$, 410 (2) $[M + H]^+$, 366 (38), 298 (16), 236 (21), 229 (26), 214 (54), 158 (68). HRMS (MALDI-TOF): calcd. for $C_{23}H_{24}NO_4S$ $[M + H]^+$ 410.1420; found 410.1520.

Bromides 6: Prepared from the corresponding alcohols **1** according to a published procedure.[17]

(*N*-Cbz-2-amino)-3-methylbutyl Bromide (6c): Yield: 77%. ^{1}H NMR: δ = 7.37–7.25 (m, 5 H), 5.12 (d, *J* = 12.6 Hz, 1 H), 5.09 (d, *J* = 12.6 Hz, 1 H), 4.98 (d, *J* = 8.7 Hz, 1 H), 3.64 (tt, *J* = 8.4, 4.2 Hz, 1 H), 3.55 (d, *J* = 3.9 Hz, 2 H), 1.88 (oct., *J* = 6.8 Hz, 1 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR: δ = 156.1, 136.4, 128.6, 128.3, 128.1, 67.0, 56.7, 37.0, 30.6, 19.4, 18.6 ppm. MS: *m*/*z* (%) = 300 (22) $[M + H]^+$, 162 (7), 108 (19), 91 (100). HRMS: calcd. for $C_{13}H_{19}NO_2{}^{81}Br$ $[M + H]^+$ 302.0579; found 302.0590. HRMS: calcd. for $C_{13}H_{19}NO_2{}^{79}Br$ $[M + H]^+$ 300.0599; found 300.0624.

Phosphonium Salts 7: A three-necked round-bottomed flask, equipped with a reflux condenser, was flushed with dry nitrogen and LiBr (0.45 g, 5.2 mmol) was added. The flask was heated a little and then charged slowly with dry CH_3CN (4.2 mL). The solution was stirred for 15 min with gentle heating till all the LiBr was dissolved. The flask was loaded dropwise over 15 min with a solution of mesylate **3** (3.5 mmol) in dry CH_3CN (1.5 mL) under an argon atmosphere. The reaction mixture was heated at reflux for 4 h, and TLC (hexane/EtOAc, 3:1) indicated that the starting material was fully consumed. The mixture was cooled to room temperature, diluted with diethyl ether, washed with saturated $NaHCO_3$ and saturated NaCl solutions. The organic layer was dried with $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography to yield clean bromide **6** in 33–77% yield. A cyclic carbamate byproduct (12–30% yield) and benzyl bromide (0.1 g, 15–30% yield) were also isolated from the column. Bromide **6** (1.0 mmol) in dry $CHCl_3$ (6.5 mL), under an argon atmosphere was treated with Ph_3P (0.66 g, 2.5 mmol). The mixture was stirred at 60 °C for 4 d, cooled to room temperature, and stirred for an additional 2 d. After evaporation of the solvent, phosphonium salt **7** was purified by chromatography (EtOAc/MeOH, 97:3) to yield a clean product (0.21 g, 38% yield). A cyclic carbamate byproduct (20–31% yield) was also isolated.

(*N*-Cbz-2-amino)propyltriphenylphosphonium Bromide (7a): Yield: 604 mg, 38% (crystallized from hexane/EtOAc, 9:1). ^{1}H NMR: δ = 7.91–7.08 (m, 20 H), 4.93 (dt, *J* = 15.3, 11.1 Hz, 1 H), 4.73 (d, *J* = 12.6 Hz, 1 H), 4.54 (d, *J* = 12.6 Hz, 1 H), 4.43 (m, 1 H), 3.28 (br. t, *J* = 13.8 Hz, 1 H), 1.52 (dd, *J* = 6.3, 2.1 Hz, 3 H) ppm. ^{13}C NMR: δ = 155.2, 136.2, 134.6 (d, *J* = 2.3 Hz), 133.8 (d, *J* = 9.8 Hz), 130.0 (d, *J* = 12.8 Hz), 128.0, 127.4, 127.3, 117.8 (d, *J* = 85.5 Hz), 65.6, 42.2 (d, *J* = 4.7 Hz), 29.4 (d, *J* = 49.4 Hz), 24.2 (d, *J* = 14.8 Hz) ppm. MS: *m*/*z* = 454 $[M]^+$, 346, 303, 262. HRMS (MALDI-TOF): calcd. for $C_{29}H_{29}NO_2P$ $[M]^+$ 454.1930; found 454.1817.

(*N*-Cbz-2-amino)butyltriphenylphosphonium Bromide (7b): Yield: 147 mg, 9%. ^{1}H NMR: δ = 7.93–7.18 (m, 20 H), 5.03 (dt, *J* = 15.3, 11.4 Hz, 1 H), 4.75 (d, *J* = 12.6 Hz, 1 H), 4.51 (d, *J* = 12.6 Hz, 1 H), 4.15 (dquint., *J* = 10.0, 5.0 Hz, 1 H), 3.13 (br. t, *J* = 14.1 Hz, 1 H), 2.07 (dquint., *J* = 13.7, 7.4 Hz, 1 H), 1.77 (dqd, *J* = 13.7, 7.4, 5.0 Hz, 1 H), 0.83 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 156.2, 136.6, 134.8 (d, *J* = 2.3 Hz), 134.1 (d, *J* = 10.5 Hz), 130.2 (d, *J* = 12.8 Hz), 128.3, 127.7, 127.6, 118.3 (d, *J* = 85.5 Hz), 66.0, 47.9 (d, *J* = 5.3 Hz), 31.2 (d, *J* = 14.6 Hz), 28.7 (d, *J* = 49.6 Hz), 10.7 ppm. MS: *m*/*z* = 468 $[M]^+$, 317. HRMS (MALDI-TOF): calcd. for $C_{30}H_{31}NO_2P$ $[M]^+$ 468.2086; found 468.2074.

(*N*-Cbz-2-amino)-3-methylbutyltriphenylphosphonium Bromide (7c): Yield: 440 mg, 26%. ^{1}H NMR: δ = 7.94–7.20 (m, 20 H), 5.16 (dt, *J* = 15.3, 11.4 Hz, 1 H), 4.77 (d, *J* = 12.6 Hz, 1 H), 4.54 (d, *J* = 12.6 Hz, 1 H), 4.00 (dtd, *J* = 13.8, 10.2, 7.2 Hz, 1 H), 2.94 (br. t, *J* = 14.4 Hz, 1 H), 2.15 (oct., *J* = 6.8 Hz, 1 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR: δ = 156.2, 136.6, 134.8 (d, *J* = 2.3 Hz), 134.1 (d, *J* = 9.8 Hz), 130.2 (d, *J* = 12.0 Hz), 128.3, 127.7, 127.6, 118.3 (d, *J* = 85.5 Hz), 66.0, 51.4 (d, *J* = 5.0 Hz), 34.9 (d, *J* = 13.2 Hz), 26.3 (d, *J* = 50.6 Hz), 19.4, 18.7 ppm. MS: *m*/*z* = 482 $[M]^+$, 374, 331. HRMS (MALDI-TOF): calcd. for $C_{31}H_3NO_2P$ $[M]^+$ 482.2243; found 482.2110.

(*N*-Cbz-2-amino)-4-methylpentyltriphenylphosphonium Bromide (7d): Yield: 503 mg, 29%. ^{1}H NMR: δ = 7.93–7.07 (m, 20 H), 7.34 (d, *J* = 10.5 Hz, 1 H), 5.00 (dt, *J* = 15.6, 11.0 Hz, 1 H), 4.75 (d, *J* = 12.6 Hz, 1 H), 4.48 (d, *J* = 12.6 Hz, 1 H), 4.35 (dquint., *J* = 10.5, 5.4 Hz, 1 H), 2.96 (br. t, *J* = 13.7 Hz, 1 H), 2.02 (m, 1 H), 1.60 (ddd, *J* = 13.6, 6.9, 6.0 Hz, 1 H), 1.49 (ddd, *J* = 13.6, 8.1, 5.4 Hz, 1 H), 0.77 (d, *J* = 6.3 Hz, 3 H), 0.69 (d, *J* = 6.3 Hz, 3 H) ppm. ^{13}C NMR: δ = 155.6, 136.3, 134.6 (d, *J* = 3.0 Hz), 133.7 (d, *J* = 10.5 Hz), 129.9 (d, *J* = 12.0 Hz), 128.1, 127.4, 127.2, 117.9 (d, *J* = 85.5 Hz), 65.7, 46.7 (d, *J* = 13.3 Hz), 44.0 (d, *J* = 4.8 Hz), 28.6 (d, *J* = 49.1 Hz), 24.5, 22.1, 21.6 ppm. MS: *m*/*z* = 496 $[M]^+$, 388, 345, 262. HRMS (MALDI-TOF): calcd. for $C_{32}H_{35}NO_2P$ $[M]^+$ 496.2399; found 496.2389.

(*N*-Cbz-2-amino)-3-phenylpropyltriphenylphosphonium Bromide (7e): Yield: 370 mg, 20% (overall). ^{1}H NMR: δ = 7.68–7.18 (m, 25 H), 5.27 (dt, *J* = 15.6, 11.1 Hz, 1 H), 4.75 (d, *J* = 12.5 Hz, 1 H), 4.70 (d, *J* = 12.5 Hz, 1 H), 4.36 (dquint., *J* = 9.5, 4.8 Hz, 1 H), 3.25 (dt, *J* = 13.5, 4.9 Hz, 1 H), 3.13 (dd, *J* = 13.5, 9.8 Hz, 1 H), 2.92 (dd, *J* = 15.6, 13.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 155.8, 137.5, 136.6, 134.8 (d, *J* = 2.3 Hz), 133.8 (d, *J* = 10.5 Hz), 130.2 (d, *J* = 12.8 Hz), 129.7, 128.9, 128.3, 128.0, 127.8, 126.9, 117.9 (d, *J* = 85.5 Hz), 66.1, 48.4 (d, *J* = 4.5 Hz), 43.9 (d, *J* = 14.3 Hz), 25.2 (d, *J* = 51.2 Hz) ppm. MS: (ESI) *m*/*z* 530 (100) $[M]^+$, 379 (31), 277 (19). HRMS (MALDI-TOF): calcd. for $C_{35}H_{33}NO_2P$ $[M]^+$ 530.2243; found 530.2279.

Synthesis of C-Terminal Building Blocks

Diols 8: A three-necked round-bottomed flask equipped with a pressure equalizing addition funnel, reflux condenser, and drying tube was flushed with argon and $LiAlH_4$ (5.7 g, 0.15 mol) was added. The flask was loaded dropwise with dry THF (100 mL). Diethyl alkylmalonate (0.1 mol) in dry THF (50 mL) was added dropwise over 1 h at room temperature by the pressure equalizing addition funnel, and the reaction mixture was heated at reflux for 3 d. The mixture was cooled to 0 °C and quenched with 0.5 M HCl (50 mL). The white suspension was diluted with water (100 mL) and its pH was adjusted to 7 with concentrated HCl. The aqueous solution was extracted with CH_2Cl_2 (3 × 300 mL). The volume of the combined organic layers was partially reduced to 100 mL under vacuum and washed with saturated $NaHCO_3$ and saturated NaCl solutions. The organic layer was dried with $MgSO_4$, filtered, and concentrated. The aqueous solution was further extracted in a continuous extraction apparatus for 5 d to give a cleaner product.

2-(Hydroxymethyl)butanol (8b): Yield: 9.98 g, 95%. ^{1}H NMR: δ = 3.79 (dd, *J* = 10.8, 3.9 Hz, 2 H), 3.63 (dd, *J* = 10.8, 7.5 Hz, 2 H), 3.49 (br. s, 2 H, OH), 1.67 (tquint., *J* = 7.0, 4.2 Hz), 1.29 (quint., *J* = 7.2 Hz, 2 H), 0.94 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 64.7, 43.8, 20.6, 11.6 ppm. MS: *m*/*z* = 105 $[M + H]^+$, 103, 86. HRMS: calcd. for $C_5H_{13}O_2$ $[M + H]^+$ 105.0916; found 105.0895.

2-Hydroxymethyl-3-methylbutanol (8c): Yield: 11.20 g, 94%. ^{1}H NMR: δ = 3.83 (dd, J = 10.8, 3.9 Hz, 2 H), 3.75 (obscured, 2 H), 3.73 (dd, J = 10.8, 8.1 Hz, 2 H), 1.72 (oct., J = 6.8 Hz, 1 H), 1.53 (qt, J = 7.6, 3.8 Hz, 1 H), 0.93 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR: δ = 64.2, 47.9, 26.4, 20.3 ppm. MS: m/z (%) = 119 (7) $[M + H]^+$, 101 (9), 83 (16). HRMS: calcd. for $C_6H_{15}O_2$ $[M + H]^+$ 119.1072; found 119.1071.

2-Hydroxymethyl-4-methylpentanol (8d): Yield: 12.25 g, 92%. ^{1}H NMR: δ = 4.24 (br. s, 2 H), 3.65 (dd, J = 10.5, 3.9 Hz, 2 H), 3.49 (dd, J = 10.5, 7.5 Hz, 2 H), 1.80 (tquint., J = 7.4, 3.6 Hz, 1 H), 1.62 (non., J = 6.7 Hz, 1 H), 1.07 (t, J = 7.2 Hz, 2 H), 0.90 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR: δ = 65.3, 39.6, 36.9, 25.3, 22.8 ppm. MS: m/z (%) = 133 (10) $[M + H]^+$, 115 (10), 97 (52). HRMS: calcd. for $C_7H_{17}O_2$ $[M + H]^+$ 133.1229; found 133.1232.

2-Benzyl-1,3-propanediol (8e): Yield: 16.21 g, 97%. ^{1}H NMR: δ = 7.29–7.13 (m, 5 H), 3.72 (dd, J = 10.8, 3.9 Hz, 2 H), 3.59 (dd, J = 10.8, 6.9 Hz, 2 H), 3.41 (s, 2 H), 2.56 (d, J = 7.5 Hz, 2 H), 2.00 (tquint., J = 7.4, 3.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 139.9, 129.1, 128.5, 126.2, 64.9, 43.9, 34.3 ppm. MS: m/z (%) = 167 (0.2) $[M + H]^+$, 148 (65), 130 (32), 104 (20), 91 (71). HRMS: calcd. for $C_{10}H_{15}O_2$ $[M + H]^+$ 167.1072; found 167.1063.

Diacetates 9: AcCl (2.6 mL, 36 mmol) was added dropwise to a stirred solution of 2-alkyl-1,3-propanediol **8** (12 mmol) in $CHCl_3$ (15 mL). After stirring at room temperature for 24 h, water (30 mL) was added, and the solution was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was washed with saturated $NaHCO_3$ and saturated NaCl solutions, dried with $MgSO_4$, filtered, and concentrated to give the clean product as a yellow oil.

2-(Acetoxymethyl)propyl Acetate (9a): Yield: 1.98 g, 94%. ^{1}H NMR: δ = 4.01 (d, J = 6.0 Hz, 4 H), 2.17 (oct., J = 6.3 Hz, 1 H), 2.07 (s, 6 H), 0.99 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR: δ = 171.2, 66.0, 32.4, 21.0, 14.0 ppm. MS: m/z (%) = 175 (12) $[M + H]^+$, 133 (22), 115 (100). HRMS: calcd. for $C_8H_{15}O_4$ $[M + H]^+$ 175.0970; found 175.0970.

2-(Acetoxymethyl)Butyl Acetate (9b): Yield: 2.0 g, 88%. ^{1}H NMR: δ = 4.03 (dd, J = 11.1, 5.4 Hz, 2 H), 3.98 (dd, J = 11.1, 6.3 Hz, 2 H), 1.99 (s, 6 H), 1.86 (ttt, J = 7.2, 6.3, 5.4 Hz, 1 H), 1.35 (quint., J = 7.4 Hz, 2 H), 0.90 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 171.1, 64.0, 38.8, 21.1, 20.9, 11.2 ppm. MS: m/z (%) = 189 (9) $[M + H]^+$, 129 (100), 103 (16), 86 (53). HRMS: calcd. for $C_9H_{17}O_4$ $[M + H]^+$ 189.1127; found 189.1165.

2-Acetoxymethyl-3-methylbutyl Acetate (9c): Yield: 2.12 g, 87%. ^{1}H NMR: δ = 4.18 (dd, J = 11.1, 4.5 Hz, 2 H), 4.06 (dd, J = 11.1, 6.3 Hz, 2 H), 2.06 (s, 6 H), 1.81 (m, 2 H), 0.97 (d, J = 6.0 Hz, 6 H) ppm. ^{13}C NMR: δ = 171.2, 63.0, 43.0, 26.9, 21.0, 20.0 ppm. MS: m/z (%) = 203 $[M + H]^+$, 143 (8), 114 (15). HRMS: calcd. for $C_{10}H_{19}O_4$ $[M + H]^+$ 203.1283; found 203.1268.

2-Acetoxymethyl-4-methylpentyl Acetate (9d): Yield: 2.35 g, 90%. ^{1}H NMR: δ = 4.08 (dd, J = 11.1, 5.1 Hz, 2), 4.01 (dd, J = 11.1, 6.3 Hz, 2 H), 2.08 (obscured, 1 H), 2.06 (s, 6 H), 1.67 (non., J = 6.7 Hz, 1 H), 1.22 (t, J = 7.2 Hz, 2 H), 0.91 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR: δ = 170.7, 64.3, 37.3, 34.9, 25.0, 22.5, 20.6 ppm. MS: m/z (%) = 217 (3) $[M + H]^+$, 216 (3) $[M]^+$, 173 (6), 157 (40), 114. HRMS: calcd. for $C_{11}H_{21}O_4$ $[M + H]^+$ 217.1440; found 217.1474.

2-(Benzyl)-1,3-propanediol Diacetate (9e): Yield: 2.89 g, 96%. ^{1}H NMR: δ = 7.30–7.12 (m, 5 H), 4.07 (dd, J = 11.1, 5.4 Hz, 2 H), 4.00 (dd, J = 11.1, 6.0 Hz, 2 H), 2.68 (d, J = 7.5 Hz, 2 H), 2.31 (ttt, J = 7.4, 6.0, 5.3 Hz, 1 H), 2.03 (s, 6 H) ppm. ^{13}C NMR: δ = 170.8, 138.7, 128.9, 128.5, 126.4, 63.7, 39.1, 34.5, 20.8 ppm. MS: m/z (%) = 251 (0.9) $[M + H]^+$, 190 (33), 131 (39), 117 (28), 104 (12), 91 (44). HRMS: calcd. for $C_{14}H_{19}O_4$ $[M + H]^+$ 251.1283; found 251.1272.

Enzymatic (Chiral) Synthesis of (*S*)-Monoacetates 10: To a stirred suspension of diester **9** (0.1–1 g) in aqueous solution containing 40 mM NaCl, 5 mM $CaCl_2$, and 0.07% BSA at pH 7.5 (2–5 mL) at 37 °C was added the enzyme lipase (from *Pseudomonas Cepacia*, 50 u/mg, 12.5–40 mg). The pH of the suspension was kept constant by the continuous addition of a 0.2 M aqueous NaOH solution by using an automatic titrator. The reaction was monitored by TLC (hexane/EtOAc, 3:1) and NMR spectroscopy. When the desired degree of conversion was reached, the reaction was quenched by the addition of ether (8 mL), and the layers were separated. The aqueous layer was further extracted with diethyl ether (3 × 15 mL), and the combined extracts were washed with saturated NaCl solution, dried with $MgSO_4$, and concentrated to give a mixture of diester starting material, the monoester product, and diol, which was separated by chromatography (hexane/EtOAc, 3:1) to give the optically active monoester product as a yellow oil. The compounds were characterized by chiral HPLC analysis.

Chemical (racemic) Synthesis of Monoacetates 10: AcCl (0.75 mL, 10.6 mmol) was slowly added by syringe to a solution of 2-alkyl-1,3-propanediol **8** (10.6 mmol) in $CHCl_3$ (8 mL), and the solution was stirred at room temperature for 30 min. Then, the mixture was diluted with water (75 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was washed with saturated $NaHCO_3$ and saturated NaCl solutions, dried with $MgSO_4$, filtered, and concentrated. Chromatography (hexane/EtOAc, 4:1) separated desired monoacetate **10** (major product) from diacetate **9** (minor product) and some diol **8** starting material.

2-(Acetoxymethyl)propanol (10a): Yield: 395 mg, 28%. ^{1}H NMR: δ = 4.08 (dd, J = 11.1, 5.7 Hz, 1 H), 4.03 (dd, J = 11.1, 6.9 Hz, 1 H), 3.56 (dd, J = 11.1, 5.4 Hz, 1 H), 3.52 (dd, J = 11.1, 5.7 Hz, 1 H), 2.21 (qquint., J = 6.9, 5.5 Hz, 1 H), 2.07 (s, 3 H), 1.06 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR: δ = 171.0, 65.9, 47.3, 35.1, 20.9, 14.8 ppm. MS: m/z (%) = 133 (20) $[M + H]^+$, 115 (34), 73 (60). HRMS: calcd. for $C_6H_{13}O_3$ $[M + H]^+$ 133.0865; found 133.0867.

2-(Acetoxymethyl)butanol (10b): Yield: 560 mg, 36%. ^{1}H NMR: δ = 4.07 (dd, J = 11.1, 5.1 Hz, 1 H), 4.01 (dd, J = 11.1, 6.3 Hz, 1 H), 3.51 (dd, J = 11.1, 4.8 Hz, 1 H), 3.44 (dd, J = 11.1, 6.3 Hz, 1 H), 2.81 (br. s, 1 H), 1.98 (s, 3 H), 1.64 (ttt, J = 6.9, 6.3, 5.1 Hz, 1 H), 1.32 (dqd, J = 13.8, 7.8, 6.9 Hz, 1 H), 1.27 (dqd, J = 13.8, 7.8, 6.9 Hz, 1 H), 0.87 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 171.7, 64.4, 62.1, 41.9, 20.8, 20.6, 11.3 ppm. MS: m/z (%) = 147 (100) $[M + H]^+$, 129 (73), 103 (15), 87 (43), 69 (73). HRMS: calcd. for $C_7H_{15}O_3$ $[M + H]^+$ 147.1021; found 147.1033.

2-Acetoxymethyl-3-methylbutanol (10c): Yield: 547 mg, 32%. ^{1}H NMR: δ = 4.25 (dd, J = 11.1, 4.8 Hz, 1 H), 4.13 (dd, J = 11.1, 6.3 Hz, 1 H), 3.68 (dd, J = 11.1, 4.8 Hz, 1 H), 3.57 (dd, J = 11.1, 6.6 Hz, 1 H), 3.03 (br. s, 1 H), 2.07 (s, 3 H), 1.81 (oct., J = 6.9 Hz, 1 H), 1.61 (qt, J = 6.6, 4.8 Hz, 1 H), 0.96 (d, J = 6.9 Hz, 3 H), 0.95 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR: δ = 171.6, 63.4, 60.9, 46.1, 26.3, 20.9, 20.2, 19.8 ppm. MS: m/z = 161 $[M + H]^+$, 143, 101. HRMS: calcd. for $C_8H_{17}O_3$ $[M + H]^+$ 161.1178; found 161.1174.

2-Acetoxymethyl-4-methylpentanol (10d): Yield: 683 mg, 41%. ^{1}H NMR: δ = 4.13 (dd, J = 11.1, 4.5 Hz, 1 H), 4.01 (dd, J = 11.1, 6.3 Hz, 1 H), 3.54 (dd, J = 11.1, 4.5 Hz, 1 H), 3.44 (dd, J = 11.1, 6.3 Hz, 1 H), 2.56 (br. s, 1 H), 2.02 (s, 3 H), 1.84 (tquint., J = 6.8, 4.5 Hz, 1 H), 1.62 (non., J = 6.8 Hz, 1 H), 1.17 (dt, J = 14.1, 7.2 Hz, 1 H), 1.08 (dt, J = 14.1, 7.2 Hz, 1 H), 0.86 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR: δ = 171.8, 64.9, 62.8, 38.1, 37.1, 25.2, 22.8,

22.7, 21.0 ppm. MS: *m*/*z* (%) = 174 $[M]^+$, 157 (100), 114 (15). HRMS: calcd. for $C_9H_{17}O_2$ $[M + H - H_2O]^+$ 157.1229; found 157.1253.

2-Benzyl-1,3-propanediol Monoacetate (10e): Yield: 1.04 g, 47%. ^1H NMR: δ = 7.32–7.16 (m, 5 H), 4.14 (dd, J = 11.4, 5.0 Hz, 1 H), 4.06 (dd, J = 11.4, 6.3 Hz, 1 H), 3.58 (dd, J = 11.1, 4.8 Hz, 1 H), 3.49 (dd, J = 11.1, 6.0 Hz, 1 H), 2.69 (dd, J = 13.8, 7.5 Hz, 1 H), 2.61 (dd, J = 13.8, 6.3 Hz, 1 H), 2.59 (s, 1 H), 2.13 (dqt, J = 7.5, 6.2, 5.0 Hz, 1 H), 2.05 (s, 3 H) ppm. ^{13}C NMR: δ = 171.6, 139.4, 129.0, 128.4, 126.1, 64.0, 61.8, 42.3, 34.2, 20.8 ppm. MS: *m*/*z* (%) = 208 $[M]^+$, 190 (5), 148 (56), 130 (55), 117 (100), 91 (30). HRMS: calcd. for $C_{12}H_{17}O_3$ $[M + H]^+$ 209.1178; found 209.1175.

Ester Aldehyde 11: Dess–Martin reagent (0.3 g, 0.68 mmol) was added to a stirred solution of 2-benzyl-1,3-propanediol monobutyrate (0.107 g, 0.45 mmol) in dry CH_2Cl_2 (40 mL) under an argon atmosphere at 0 °C. The ice bath was removed, and the reaction mixture was allowed to proceed at room temperature for 3.5 h. CH_2Cl_2 (30 mL) was added, and the mixture was washed with saturated $Na_2S_2O_5$ solution (50 mL). The layers were separated, and the organic layer was washed with saturated $NaHCO_3$ (2×) and saturated NaCl solutions, dried with $MgSO_4$, and filtered. Evaporation of the solvent afforded the clean aldehyde as a yellow oil (90 mg, 85% yield). ^1H NMR: δ = 9.74 (d, J = 1.5 Hz, 1 H), 7.30–7.15 (m, 5 H), 4.32 (dd, J = 11.7, 4.5 Hz, 1 H), 4.24 (dd, J = 11.4, 6.2 Hz, 1 H), 3.09 (dd, J = 13.5, 6.3 Hz, 1 H), 2.910 (qdd, J = 6.0, 4.5, 1.5 Hz, 1 H), 2.78 (dd, J = 13.5, 8.1 Hz, 1 H), 2.27 (t, J = 7.2 Hz, 2 H), 1.63 (sext., J = 7.5 Hz, 2 H), 0.94 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 201.5, 173.4, 137.7, 129.0, 128.8, 126.8, 61.4, 52.6, 36.0, 31.8, 18.4, 13.7 ppm.

Acetyl Mesylates 12: A solution of monoacetate **10** (6.0 mmol) and Et_3N (1.25 mL, 8.9 mmol) in dry CH_2Cl_2 (10 mL) under an argon atmosphere was cooled to 0 °C. The solution was stirred for 15 min, followed by slow addition (10 min) of MsCl (0.7 mL, 9.0 mmol) in dry CH_2Cl_2 (2 mL). Stirring was continued at 0 °C under an argon atmosphere for 3 h. The solution turned yellow. Ether was added, and the solution was washed with 1 N HCl, saturated $NaHCO_3$, and saturated NaCl solutions. The organic phase was dried with $MgSO_4$, filtered, and concentrated to give the clean product.

2-(Acetoxymethyl)butanol Methanesulfonate (12b): Yield: 1.27 g, 94%. ^1H NMR: δ = 4.25 (dd, J = 9.9, 5.1 Hz, 1 H), 4.21 (dd, J = 9.9, 5.7 Hz, 1 H), 4.15 (dd, J = 11.4, 5.1 Hz, 1 H), 4.06 (dd, J = 11.4, 6.6 Hz, 1 H), 3.03 (s, 3 H), 2.07 (s, 3 H), 2.01 (qq, J = 6.9, 5.1 Hz, 1 H), 1.49 (dqd, J = 13.8, 7.8, 6.3 Hz, 1 H), 1.43 (ddq, J = 13.8, 9.3, 6.9 Hz, 1 H), 0.99 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 170.9, 69.0, 63.1, 39.3, 37.2, 20.9, 20.6, 11.2 ppm. MS: *m*/*z* (%) = 225 (100) $[M + H]^+$, 129 (57). HRMS: calcd. for $C_8H_{17}O_5S$ $[M + H]^+$ 225.0797; found 225.0781.

3-Acetoxy-2-benzyl-1-propyl Methanesulfonate (12e): Yield: 1.72 g, 100%. ^1H NMR: δ = 7.33–7.16 (m, 5 H), 4.20 (dd, J = 9.8, 5.0 Hz, 1 H), 4.14 (dd, J = 9.8, 5.6 Hz, 1 H), 4.13 (dd, J = 11.4, 5.1 Hz, 1 H), 4.02 (dd, J = 11.4, 6.6 Hz, 1 H), 2.97 (s, 3 H), 2.74 (dd, J = 14.3, 7.9 Hz, 1 H), 2.70 (dd, J = 14.3, 7.2 Hz, 1 H), 2.39 (qq, J = 7.2, 5.2 Hz, 1 H), 2.06 (s, 3 H) ppm. ^{13}C NMR: δ = 170.7, 137.9, 128.9, 128.6, 126.6, 68.6, 62.8, 39.5, 37.0, 33.8, 20.7 ppm. MS: *m*/*z* (%) = 287 (1.4) $[M + H]^+$, 226 (3), 190 (18), 130 (100), 91 (4). HRMS: calcd. for $C_{13}H_{19}O_5S$ $[M + H]^+$ 287.0953; found 287.0957.

Sulfides 13: Thiophenol or 1-phenyl-1*H*-tetrazole-5-thiol (2.5 mmol) was dissolved in dry THF (4 mL). NaH (60% in mineral oil, either 1 or 2 equiv. relative to the thiol to provide either the acetoxy or hydroxy sulfide, respectively) was added slowly, and the white suspension was stirred at room temperature for 15 min. A solution of mesylate **12** (0.83 mmol) in dry THF (1.5 mL) was added, and the mixture was stirred overnight at 50 °C. The mixture was cooled to room temperature, diluted with CH_2Cl_2 (15 mL), and washed with 10% NaOH solution (20 mL). The aqueous phase was re-extracted with CH_2Cl_2 (3 × 20 mL), and the volume of the combined organic phase was washed with saturated NaCl solution, dried with $MgSO_4$, filtered, and evaporated to provide a yellow oil. Chromatography (hexane/EtOAc, 9:1) afforded the clean product.

2-Hydroxymethylbutyl Phenyl Sulfide (13′b): Yield: 140 mg, 86%. ^1H NMR: δ = 7.34 (d, J = 8.4 Hz, 2 H), 7.26 (t, J = 8.1 Hz, 2 H), 7.14 (tt, J = 7.2, 1.5 Hz, 1 H), 3.70 (dd, J = 11.0, 4.7 Hz, 1 H), 3.61 (dd, J = 11.0, 5.9 Hz, 1 H), 3.01 (dd, J = 12.9, 6.9 Hz, 1 H), 2.96 (dd, J = 12.9, 5.7 Hz, 1 H), 2.16 (s, 1 H), 1.70 (dsext., J = 6.4, 4.8 Hz, 1 H), 1.46 (quint., J = 7.2 Hz, 2 H), 0.91 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 137.0, 128.9, 125.8, 64.0, 41.8, 35.3, 23.3, 11.3 ppm. MS: *m*/*z* (%) = 197 (19) $[M + H]^+$, 196 (100) $[M]^+$, 123 (27), 110 (64). HRMS: (DCI/CH_4): calcd. for $C_{11}H_{16}OS$ $[M]^+$ 196.0922; found 196.0899.

(2-Acetoxymethylbutyl) 1-Phenyl-1*H*-tetrazole-5-yl Sulfide (13b$_1$): Yield: 227 mg, 89%. ^1H NMR: δ = 7.60–7.51 (m, 5 H), 4.19 (dd, J = 11.3, 4.8 Hz, 1 H), 4.09 (dd, J = 11.3, 6.0 Hz, 1 H), 3.55 (dd, J = 13.2, 5.7 Hz, 1 H), 3.44 (dd, J = 13.2, 7.2 Hz, 1 H), 2.14 (tqd, J = 7.2, 6.0, 4.8 Hz, 1 H), 2.06 (s, 3 H), 1.56 (dqd, J = 14.1, 7.2, 6.3 Hz, 1 H), 1.50 (dquint., J = 14.1, 7.2 Hz, 1 H), 0.99 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 171.0, 154.3, 133.6, 130.2, 129.8, 127.9, 64.7, 39.0, 34.9, 23.5, 20.9, 11.1 ppm. MS: *m*/*z* (%) = 307 (100) $[M + H]^+$, 129 (21), 118 (25). HRMS: calcd. for $C_{14}H_{19}N_4O_2S$ $[M + H]^+$ 307.1229; found 307.1242.

(2-Hydroxymethylbutyl) 1-Phenyl-1*H*-tetrazole-5-yl Sulfide (13′b$_1$): Yield: 207 mg, 94%. ^1H NMR: δ = 7.63–7.56 (m, 5 H), 3.72 (dd, J = 11.9, 3.9 Hz, 1 H), 3.60 (dd, J = 14.1, 4.7 Hz, 1 H), 3.56 (dd, J = 11.9, 6.9 Hz, 1 H), 3.49 (dd, J = 14.1, 6.6 Hz, 1 H), 3.38 (br. s, 1 H), 1.94 (tquint., J = 6.9, 4.2 Hz, 1 H), 1.51 (dquint., J = 14.0, 7.5 Hz, 1 H), 1.44 (dquint., J = 14.0, 7.0 Hz, 1 H), 0.97 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 155.7, 133.6, 130.4, 129.9, 124.0, 62.3, 43.1, 34.9, 23.0, 11.6 ppm. MS: *m*/*z* (%) = 265 (100) $[M + H]^+$, 118 (45). HRMS: calcd. for $C_{12}H_{17}N_4OS$ $[M + H]^+$ 265.1123; found 265.1109.

3-Acetoxy-2-benzylpropyl Phenyl Sulfide (13e): Yield: 187 mg, 78% yield (crystallized from hexane/EtOAc, 9:1). ^1H NMR: δ = 7.27–7.10 (m, 10 H), 4.14 (dd, J = 11.1, 5.1 Hz, 1 H), 4.05 (dd, J = 11.1, 5.4 Hz, 1 H), 2.94 (d, J = 6.6 Hz, 2 H), 2.81 (dd, J = 13.8, 7.2 Hz, 1 H), 2.72 (dd, J = 13.8, 7.5 Hz, 1 H), 2.21 (ttt, J = 7.2, 6.6, 5.3 Hz, 1 H), 2.02 (s, 3 H) ppm. ^{13}C NMR: δ = 171.0, 139.1 136.4, 129.3, 129.2, 129.0, 128.6, 126.5, 126.1, 65.3, 39.7, 37.0, 34.9, 21.0 ppm. MS: *m*/*z* (%) = 300 (48) $[M]^+$, 191 (9), 149 (45), 110 (47), 91 (94). HRMS: calcd. for $C_{18}H_{20}O_2S$ $[M]^+$ 300.1184; found 300.1189.

2-Benzyl-3-hydroxypropyl Phenyl Sulfide (13′e): Yield: 212 mg, 99%. ^1H NMR: δ = 7.27–7.05 (m, 10 H), 3.62 (dd, J = 11.0, 4.8 Hz, 1 H), 3.53 (dd, J = 11.0, 5.4 Hz, 1 H), 2.94 (dd, J = 13.5, 6.6 Hz, 1 H), 2.89 (dd, J = 13.5, 6.6 Hz, 1 H), 2.70 (d, J = 7.2 Hz, 2 H), 2.30 (br. s, 1 H), 2.01 (sept., J = 6.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 139.7, 136.5, 129.2, 128.9, 128.7, 128.4, 126.1, 125.7, 63.6, 42.3, 36.7, 34.4 ppm.

(3-Acetoxy-2-benzylpropyl) 1-Phenyl-1*H*-tetrazole-5-yl Sulfide (13e$_1$): Yield: 260 mg, 85%. ^1H NMR: δ = 7.59–7.53 (m, 5 H), 7.32–7.15 (m, 5 H), 4.15 (dd, J = 11.4, 4.8 Hz, 1 H), 4.00 (dd, J = 11.4, 5.7 Hz, 1 H), 3.54 (dd, J = 13.2, 6.0 Hz, 1 H), 3.45 (dd, J = 13.2, 6.9 Hz, 1 H), 2.86 (dd, J = 13.8, 6.6 Hz, 1 H), 2.75 (dd, J = 13.8, 7.8 Hz, 1 H), 2.54 (qtd, J = 7.1, 5.7, 4.7 Hz, 1 H), 2.07 (s, 3

H) ppm. ^{13}C NMR: δ = 170.9, 154.1, 138.3, 133.6, 130.3, 129.9, 129.1, 128.7, 126.7, 123.9, 64.3, 39.4, 36.9, 34.8, 20.9 ppm. MS: *m*/*z* (%) = 369 (100) [M + H]$^+$, 327 (13), 222 (16), 191 (95), 163 (66), 131 (53), 91 (23). HRMS: calcd. for $C_{19}H_{21}N_4O_2S$ [M + H]$^+$ 369.1385; found 369.1351.

(2-Benzyl-3-hydroxypropyl) 1-Phenyl-1*H*-tetrazole-5-yl Sulfide (13′e$_1$): Yield: 230 mg, 85%. ^{1}H NMR: δ = 7.55 (s, 5 H), 7.26–7.15 (m, 5 H), 3.95 (br. s, 1 H), 3.71 (dd, *J* = 12.0, 3.9 Hz, 1 H), 3.55 (dd, *J* = 12.0, 6.3 Hz, 1 H), 3.52 (dd, *J* = 14.1, 4.5 Hz, 1 H), 3.41 (dd, *J* = 14.1, 6.9 Hz, 1 H), 2.79 (dd, *J* = 13.8, 7.2 Hz, 1 H), 2.68 (dd, *J* = 13.8, 7.8 Hz, 1 H), 2.32 (m, 1 H) ppm. ^{13}C NMR: δ = 155.4, 139.0, 133.3, 130.3, 129.8, 129.0, 128.5, 126.3, 123.8, 61.9, 43.2, 36.3, 34.4 ppm. MS: *m*/*z* (%) = 327 (43) [M + H]$^+$, 236 (13), 180 (77), 163 (15), 131 (26), 118 (34), 91 (100). HRMS: calcd. for $C_{17}H_{19}N_4OS$ [M + H]$^+$ 327.1279; found 327.1253.

Sulfones 14: *m*-CPBA (75%, 0.28 g, 1.6 mmol) was added to a stirred solution of sulfide **13** (0.5 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C. The ice bath was removed, and the reaction mixture was allowed to proceed at room temperature for 3 h. CH_2Cl_2 (10 mL) was added, and the mixture was washed with saturated $Na_2S_2O_5$/10% NaOH solution (1:1, 10 mL). The layers were separated, and the aqueous phase was further extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with saturated $NaHCO_3$ and saturated NaCl solutions, dried with $MgSO_4$, filtered, and concentrated to give a yellow oil, which was purified by chromatography (hexane/EtOAc, 4:1) to afford the clean product.

2-Hydroxymethylbutyl Phenyl Sulfone (14′b): Yield: 102 mg, 89%. ^{1}H NMR: δ = 7.93 (d, *J* = 7.2 Hz, 2 H), 7.66 (tt, *J* = 7.4, 1.5 Hz, 1 H), 7.57 (tt, *J* = 7.4, 1.5 Hz, 2 H), 3.80 (dd, *J* = 11.1, 4.5 Hz, 1 H), 3.59 (dd, *J* = 11.1, 5.4 Hz, 1 H), 3.33 (dd, *J* = 14.1, 7.2 Hz, 1 H), 3.03 (dd, *J* = 14.1, 4.8 Hz, 1 H), 2.56 (br. s, 1 H), 2.08 (qq, *J* = 6.8, 5.1 Hz, 1 H), 1.51 (dqd, *J* = 13.8, 7.2, 6.3 Hz, 1 H), 1.46 (dqd, *J* = 13.8, 6.6, 5.7 Hz, 1 H), 0.86 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 139.8, 133.8, 129.4, 127.8, 63.3, 57.4, 37.7, 24.1, 11.0 ppm. MS: *m*/*z* (%) = 229 (100) [M + H]$^+$, 211 (22), 171 (8), 143 (64), 125 (22). HRMS: calcd. for $C_{11}H_{17}O_3S$ [M + H]$^+$ 229.0898; found 229.0883.

(3-Acetoxybutyl) 1-Phenyl-1*H*-tetrazole-5-yl Sulfone (14b$_1$): ^{1}H NMR: δ = 7.69–7.59 (m, 5 H), 4.26 (dd, *J* = 11.4, 4.8 Hz, 1 H), 4.14 (dd, *J* = 11.4, 5.4 Hz, 1 H), 3.95 (dd, *J* = 14.4, 6.6 Hz, 1 H), 3.76 (dd, *J* = 14.4, 5.7 Hz, 1 H), 2.48 (sept., *J* = 6.0 Hz, 1 H), 2.08 (s, 3 H), 1.69 (dqd, *J* = 14.6, 7.8, 5.9 Hz, 1 H), 1.60 (dquint., *J* = 14.6, 7.3 Hz, 1 H), 0.99 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR: δ = 170.8, 153.9, 133.1, 131.6, 129.8, 125.2, 64.3, 57.0, 34.4, 24.2, 20.9, 10.9 ppm.

3-Acetoxy-2-benzylpropyl Phenyl Sulfone (14e): Yield: 127 mg, 76%. ^{1}H NMR: δ = 7.84 (d, *J* = 7.8 Hz, 2 H), 7.64 (tt, *J* = 7.5, 1.4 Hz, 1 H), 7.53 (tt, *J* = 7.5, 1.4 Hz, 2 H), 7.27–7.03 (m, 5 H), 4.12 (dd, *J* = 11.3, 5.0 Hz, 1 H), 4.03 (dd, *J* = 11.3, 5.0 Hz, 1 H), 3.23 (dd, *J* = 14.6, 6.5 Hz, 1 H), 3.09 (dd, *J* = 14.6, 5.6 Hz, 1 H), 2.83 (dd, *J* = 13.8, 7.2 Hz, 1 H), 2.74 (dd, *J* = 13.8, 7.5 Hz, 1 H), 2.54 (tdq, *J* = 7.4, 6.5, 5.1 Hz, 1 H), 2.01 (s, 3 H) ppm. ^{13}C NMR: δ = 170.7, 139.4, 137.7, 133.8, 129.4, 129.1, 128.7, 127.9, 126.7, 64.8, 56.3, 37.2, 35.1, 20.8 ppm. MS: *m*/*z* (%) = 333 (2) [M + H]$^+$, 273 (5), 131 (100), 117 (10), 91 (30). HRMS: calcd. for $C_{18}H_{21}O_4S$ [M + H]$^+$ 333.1161; found 333.1139.

2-Benzyl-3-hydroxypropyl Phenyl Sulfone (14′e): Yield: 138 mg, 95%. ^{1}H NMR: δ = 7.81 (d, *J* = 7.8 Hz, 2 H), 7.56 (t, *J* = 7.5 Hz, 1 H), 7.47 (t, *J* = 7.8 Hz, 2 H), 7.25–7.02 (m, 5 H), 3.76 (dd, *J* = 11.1, 4.5 Hz, 1 H), 3.57 (dd, *J* = 11.1, 5.1 Hz, 1 H), 3.33 (dd, *J* = 14.4, 7.2 Hz, 1 H), 3.03 (dd, *J* = 14.4, 5.4 Hz, 1 H), 2.77 (dd, *J* = 13.8, 7.8 Hz, 1 H), 2.76 (obscured, 1 H), 2.72 (dd, *J* = 13.8, 7.2 Hz, 1 H), 2.37 (qq, *J* = 7.3, 4.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 139.3, 138.4, 133.6, 129.3, 129.1, 128.5, 127.6, 126.4, 62.9, 56.1, 37.8, 36.1 ppm. MS: *m*/*z* (%) = 291 (13) [M + H]$^+$, 273 (13), 131 (100), 117 (26), 104 (6), 91 (43). HRMS: calcd. for $C_{16}H_{19}O_3S$ [M + H]$^+$ 291.1055; found 291.1058.

(3-Acetoxy-2-benzylpropyl) 1-Phenyl-1*H*-tetrazole-5-yl Sulfone (14e$_1$): Yield: 183 mg, 91%. ^{1}H NMR: δ = 7.63–7.12 (m, 10 H), 4.20 (dd, *J* = 11.4, 4.2 Hz, 1 H), 4.02 (dd, *J* = 11.4, 4.8 Hz, 1 H), 3.94 (dd, *J* = 15.0, 6.0 Hz, 1 H), 3.73 (dd, *J* = 15.0, 5.4 Hz, 1 H), 2.96 (dd, *J* = 16.8, 9.6 Hz, 1 H), 2.84 (m, 1 H), 2.83 (dd, *J* = 16.8, 8.1 Hz, 1 H), 2.06 (s, 3 H) ppm. ^{13}C NMR: δ = 170.6, 153.7, 137.2, 132.9, 131.5, 129.7, 129.2, 128.8, 127.0, 125.2, 64.0, 56.5, 37.1, 34.7, 20.7 ppm. MS: *m*/*z* (%) = 401 (28) [M + H]$^+$, 359 (7), 208 (23), 118 (62), 91 (100). HRMS: calcd. for $C_{19}H_{21}N_4O_4S$ [M + H]$^+$ 401.1284; found 401.1285.

Acetyl Bromides 15: Prepared as described above for N-terminal bromides **6**.

2-Acetoxymethylbutyl Bromide (15b): Yield: 79%. ^{1}H NMR: δ = 4.15 (dd, *J* = 11.1, 5.1 Hz, 1 H), 4.03 (dd, *J* = 11.1, 7.2 Hz, 1 H), 3.53 (dd, *J* = 10.4, 4.8 Hz, 1 H), 3.48 (dd, *J* = 10.4, 5.1 Hz, 1 H), 2.07 (s, 3 H), 1.92 (qq, *J* = 7.0, 4.9 Hz, 1 H), 1.49 (dquint., *J* = 13.8, 7.4 Hz, 1 H), 1.43 (dquint., *J* = 13.8, 7.2 Hz, 1 H), 0.96 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR: δ = 170.6, 64.7, 40.7, 34.9, 22.4, 20.7, 10.9 ppm. MS: *m*/*z* (%) = 211, 209 (9, 6) [M + H]$^+$, 149 (11), 129 (8), 85 (82), 71 (100). HRMS: calcd. for $C_7H_{14}O_2{}^{81}Br$ [M + H]$^+$ 211.0157; found 211.0122. HRMS: calcd. for $C_7H_{14}O_2{}^{79}Br$ [M + H]$^+$ 209.0177; found 209.0126.

3-Acetoxy-2-benzylpropyl Bromide (15e): Yield: 93%. ^{1}H NMR: δ = 7.35–7.15 (m, 5 H), 4.14 (dd, *J* = 11.1, 5.4 Hz, 1 H), 4.04 (dd, *J* = 11.1, 6.9 Hz, 1 H), 3.46 (dd, *J* = 10.2, 4.5 Hz, 1 H), 3.34 (dd, *J* = 10.2, 5.1 Hz, 1 H), 2.74 (dd, *J* = 14.2, 7.8 Hz, 1 H), 2.69 (dd, *J* = 14.2, 6.6 Hz, 1 H), 2.28 (tdq, *J* = 7.5, 6.9, 5.0 Hz, 1 H), 2.05 (s, 3 H) ppm. ^{13}C NMR: δ = 170.7, 138.3, 129.1, 128.6, 126.6, 64.8, 41.1, 35.6, 34.8, 20.8 ppm. MS: *m*/*z* (%) = 273, 271 (5, 4) [M + H]$^+$, 212, 210 (9, 11), 131 (100), 91 (26). HRMS: calcd. for $C_{12}H_{16}O_2{}^{81}Br$ [M + H]$^+$ 273.0313; found 273.0403. HRMS: calcd. for $C_{12}H_{16}O_2{}^{79}Br$ [M + H]$^+$ 271.0334; found 271.0330.

Hydroxy Bromides 15′: Acetyl bromide **15** (4.0 mmol) was dissolved in dry THF (18 mL) and cooled to –78 °C under an argon atmosphere. DIBAL-H (1 M in hexane, 20 mL) was added dropwise over 15 min. After an additional 1.5 h at –78 °C, the reaction was quenched with EtOAc (5 mL) and water (3 mL). The mixture was filtered through Celite, washed with diethyl ether and EtOAc, dried with $MgSO_4$, and filtered. Evaporation of the solvent afforded the clean product as a brownish oil.

2-Hydroxymethylbutyl Bromide (15′b): Yield: 670 mg, 100%. ^{1}H NMR: δ = 3.69 (dd, *J* = 11.0, 5.0 Hz, 1 H), 3.61 (dd, *J* = 9.9, 4.2 Hz, 1 H), 3.58 (dd, *J* = 11.0, 7.1 Hz, 1 H), 3.52 (dd, *J* = 9.9, 5.4 Hz, 1 H), 3.31 (s, 1 H), 1.73 (qq, *J* = 6.9, 4.9 Hz, 1 H), 1.41 (quint., *J* = 7.3 Hz, 2 H), 0.94 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 63.0, 43.7, 35.9, 22.1, 11.2 ppm. MS: *m*/*z* (%) = 169 and 167 (6 and 5) [M + H]$^+$, 151 and 149 (7 and 8), 87 (11). HRMS: calcd. for $C_5H_{12}O^{81}Br$ [M + H]$^+$ 169.0051; found 169.0027. HRMS: calcd. for $C_5H_{12}O^{79}Br$ [M + H]$^+$ 167.0072; found 167.0090.

2-Benzyl-3-hydroxypropyl Bromide (15′e): Yield: 916 mg, 100%. ^{1}H NMR: δ = 7.32–7.17 (m, 5 H), 3.69 (dd, *J* = 11.1, 5.1 Hz, 1 H), 3.62 (dd, *J* = 11.1, 6.9 Hz, 1 H), 3.55 (dd, *J* = 10.1, 4.4 Hz, 1 H), 3.40 (dd, *J* = 10.1, 5.3 Hz, 1 H), 2.71 (dd, *J* = 13.7, 7.2 Hz, 1 H), 2.66 (dd, *J* = 13.7, 7.5 Hz, 1 H), 2.19 (s, 1 H), 2.11 (qq, *J* = 7.1, 4.9 Hz, 1 H) ppm. ^{13}C NMR: δ = 139.1, 129.2, 128.6, 126.5, 63.3,

44.2, 35.8, 35.6 ppm. MS: *m*/*z* (%) = 230 and 228 (14 and 16) $[M]^+$, 212 and 210 (48 and 51), 131 (95), 117 (12), 91 (100). HRMS: calcd. for $C_{10}H_{13}O^{81}Br$ $[M]^+$ 230.0129; found 230.0058. HRMS: calcd. for $C_{10}H_{13}O^{79}Br$ $[M]^+$ 228.0150; found 228.0117.

Phosphonium Salts 16: Ph_3P (0.34 g, 1.31 mmol) under an argon atmosphere was heated to 120 °C. Bromide **15** (1.31 mmol) was added to the melted Ph_3P, and the reaction mixture was stirred at 120 °C for 2 d. The mixture was cooled to room temperature, and the brownish residue was chromatographed (EtOAc/hexane, 1:1 and then EtOAc/MeOH, 97:3) to give the clean phosphonium salt as a yellowish solid.

(2-Benzyl-3-hydroxypropyl)triphenylphosphonium Bromide (16′e): Yield: 323 mg, 60% (20% recovery of starting material). ^{1}H NMR: δ = 7.83–6.88 (m, 20 H), 4.48 (ddd, *J* = 16.1, 13.9, 5.0 Hz, 1 H), 3.53 (dd, *J* = 11.4, 5.7 Hz, 1 H), 3.47 (dd, *J* = 11.4, 6.0 Hz, 1 H), 2.90 (ddd, *J* = 16.1, 13.2, 5.6 Hz, 1 H), 2.67 (dd, *J* = 13.3, 8.3 Hz, 1 H), 2.37 (dd, *J* = 13.3, 6.3 Hz, 1 H), 2.25 (m, 1 H) ppm. ^{13}C NMR: δ = 138.2, 134.7 (d, *J* = 2.3 Hz), 133.3 (d, *J* = 10.5 Hz), 130.2 (d, *J* = 12.8 Hz), 128.8, 128.3, 126.2, 118.2 (d, *J* = 84.8 Hz), 62.4 (d, *J* = 7.2 Hz), 38.4 (d, *J* = 6.5 Hz), 37.8 (d, *J* = 3.6 Hz), 23.1 (d, *J* = 50.3 Hz) ppm. MS: *m*/*z* (%) = 411 (8) $[M]^+$, 393 (100), 277 (7). HRMS: calcd. for $C_{28}H_{28}OP$ $[M]^+$ 411.1878; found 411.1876.

Diethyl 3-Acetoxy-2-benzylpropylphosphonate (17e): A mixture of $P(OEt)_3$ (1.9 mL, 10.9 mmol) and bromide **15e** (1.5 g, 5.4 mmol) under an argon atmosphere was heated to 140 °C under Hickman condenser for 20 h. The mixture was cooled to room temperature, and the residue was chromatographed (EtOAc/hexane, 1:1 and then EtOAc/MeOH, 97:3) to afford the desired product as a yellowish oil (0.89 g, 50% yield; 20% recovery of starting material). ^{1}H NMR: δ = 7.35–7.16 (m, 5 H), 4.18–3.98 (m, 6 H), 2.84 (dd, *J* = 13.5, 6.9 Hz, 1 H), 2.75 (dd, *J* = 13.5, 7.1 Hz, 1 H), 2.42 (sept., *J* = 7.0 Hz, 1 H), 2.06 (s, 3 H), 1.84 (ddd, *J* = 22.8, 15.6, 7.2 Hz, 1 H), 1.78 (ddd, *J* = 21.9, 15.6, 6.9 Hz, 1 H), 1.31 (t, *J* = 7.2 Hz, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR: δ = 170.9, 138.9, 129.3, 128.5, 126.5, 66.1 (d, *J* = 8.9 Hz), 61.6 (d, *J* = 6.3 Hz), 38.4 (d, *J* = 10.4 Hz), 34.9 (d, *J* = 3.8 Hz), 26.8 (d, *J* = 140.1 Hz), 20.9, 16.44 (d, *J* = 6.1 Hz) ppm. MS: *m*/*z* = 329 $[M + H]^+$, 287, 269, 283, 328.

Silyl Acetates 18: 2-(Alkyl)-1,3-propanediol monoacetate **10** (27 mmol) in dry DMF (20 mL) was added to a solution of imidazole (2.7 g, 39.5 mmol) and *tert*-butylchlorodimethylsilane (6.0 g, 39.5 mmol) in dry DMF (60 mL). After stirring overnight at room temperature, the mixture was diluted with diethyl ether (100 mL) and water (50 mL) and the layers were separated. The aqueous phase was further extracted with CH_2Cl_2 (3 × 75 mL), and the combined organic layer was washed with water and brine, dried with $MgSO_4$, and filtered. Evaporation of the solvent afforded the clean product as a yellow oil.

(2-Acetoxymethylbutoxy) *tert*-Butyldimethylsilane (18b): Yield: 6.77 g, 96%. ^{1}H NMR: δ = 4.04 (dd, *J* = 11.1, 6.0 Hz, 1 H), 4.01 (dd, *J* = 11.1, 5.7 Hz, 1 H), 3.56 (dd, *J* = 9.9, 4.8 Hz, 1 H), 3.51 (dd, *J* = 9.9, 5.7 Hz, 1 H), 2.00 (s, 3 H), 1.66 (ttt, *J* = 6.9, 6.0, 5.1 Hz, 1 H), 1.36 (dqd, *J* = 13.8, 7.8, 6.9 Hz, 1 H), 1.29 (dquint., *J* = 13.8, 7.1 Hz, 1 H), 0.88 (t, *J* = 7.5 Hz, 3 H), 0.84 (s, 9 H), –0.01 (s, 6 H) ppm. ^{13}C NMR: δ = 171.2, 64.5, 62.3, 41.9, 25.9, 21.0, 20.8, 18.3, 11.5, –5.5 ppm. MS: *m*/*z* (%) = 261 (4) $[M + H]^+$, 201 (9), 129 (8). HRMS: calcd. for $C_{13}H_{29}O_3Si$ $[M + H]^+$ 261.1886; found 261.1880.

(3-Acetoxy-2-benzylpropoxy) *tert*-Butyldimethylsilane (18e): Yield: 8.64 g, 99%. ^{1}H NMR: δ = 7.35–7.19 (m, 5 H), 4.10 (d, *J* = 6.0 Hz, 2 H), 3.62 (dd, *J* = 9.9, 4.8 Hz, 1 H), 3.55 (dd, *J* = 9.9, 5.1 Hz, 1 H), 2.75 (dd, *J* = 13.7, 7.7 Hz, 1 H), 2.64 (dd, *J* = 13.7, 7.1 Hz, 1 H), 2.14 (sept., *J* = 6.1 Hz, 1 H), 2.06 (s, 3 H), 0.95 (s, 9 H), 0.07 (s, 6 H) ppm. ^{13}C NMR: δ = 171.0, 139.8, 129.1, 128.4, 126.1, 64.3, 61.8, 42.2, 34.2, 25.9, 20.9, 18.3, –5.5, –5.6 ppm. MS: *m*/*z* (%) = 323 (7) $[M + H]^+$, 265 (22), 263 (21), 191 (21), 131 (100), 117 (92), 91 (27). HRMS: calcd. for $C_{18}H_{31}O_3Si$ $[M + H]^+$ 323.2042; found 323.2082.

Hydroxysilanes 18′: Na_2CO_3 (1.5 g) was added to a stirred solution of acetate **18** (3.0 mmol) in dry MeOH (60 mL). The suspension was stirred vigorously at room temperature for 1.5 h and was stopped when TLC (hexane/EtOAc, 5:1) indicated that the starting material was fully consumed. The mixture was filtered off by suction filtration to remove the Na_2CO_3 and washed with methanol and ether. The filtrate was evaporated to dryness, and the residue was dissolved in ether. The ether phase was washed with acidic water (pH 2.5, 3 × 80 mL) until the pH of the aqueous layer was neutral. Then the ether phase was washed with saturated NaCl solution, dried with $MgSO_4$, filtered, and concentrated to give the desired product as a yellow oil.

(2-Hydroxymethylbutoxy) *tert*-Butyldimethylsilane (18′b): Yield: 540 mg, 82%. ^{1}H NMR: δ = 3.61 (dd, *J* = 9.9, 4.5 Hz, 1 H), 3.53 (dd, *J* = 10.8, 4.2 Hz, 1 H), 3.48 (dd, *J* = 9.9, 6.9 Hz, 1 H), 3.46 (dd, *J* = 10.8, 6.9 Hz, 1 H), 3.33 (br. s, 1 H), 1.47 (tquint., *J* = 6.8, 4.4 Hz, 1 H), 1.20 (dqd, *J* = 13.8, 7.8, 5.7 Hz, 1 H), 1.15 (ddq, *J* = 13.8, 8.1, 6.9 Hz, 1 H), 0.79 (t, *J* = 7.4 Hz, 3 H), 0.76 (s, 9 H), –0.07 (s, 6 H) ppm. ^{13}C NMR: δ = 65.7, 64.9, 43.9, 25.7, 20.4, 18.0, 11.5, –5.7, –5.8 ppm. MS: *m*/*z* (%) = 219 (26) $[M + H]^+$, 201 (7), 189 (38), 161 (24), 87 (7), 73 (22). HRMS: calcd. for $C_{11}H_{27}O_2Si$ $[M + H]^+$ 219.1780; found 219.1741.

2-Benzyl-3-hydroxypropoxy *tert*-Butyldimethylsilane (18′e): Yield: 743 mg, 92%. ^{1}H NMR: δ = 7.35–7.16 (m, 5 H), 3.77 (dd, *J* = 9.9, 4.2 Hz, 1 H), 3.75 (dd, *J* = 10.7, 3.8 Hz, 1 H), 3.65 (dd, *J* = 10.7, 6.5 Hz, 1 H), 3.65 (dd, *J* = 9.9, 6.3 Hz, 1 H), 2.93 (br. s, 1 H), 2.68 (dd, *J* = 13.5, 7.8 Hz, 1 H), 2.63 (dd, *J* = 13.5, 5.4 Hz, 1 H), 2.02 (ttt, *J* = 7.5, 6.5, 3.9 Hz, 1 H), 0.95 (s, 9 H), 0.09 (s, 3 H), 0.09 (s, 3 H) ppm. ^{13}C NMR: δ = 140.2, 129.1, 128.4, 126.0, 65.6, 65.2, 44.2, 34.2, 25.9, 18.2, –5.5 ppm. MS: *m*/*z* (%) = 269 $[M + H]^+$, 131 (100), 117 (10), 105 (21), 91 (46). HRMS: calcd. for $C_{15}H_{29}O_2Si$ $[M + H]^+$ 269.1937; found 269.1936.

Silyl Aldehydes 19

(2-Formylbutoxy) *tert*-Butyldimethylsilane (19b): Dess–Martin reagent (0.6 g, 1.37 mmol) was added to a stirred solution of alcohol **18′b** (0.2 g, 0.92 mmol) in dry CH_2Cl_2 (70 mL) under an argon atmosphere at 0 °C. The ice bath was removed, and the reaction mixture was allowed to proceed at room temperature for 3.5 h. CH_2Cl_2 (60 mL) was added, and the mixture was washed with saturated $Na_2S_2O_5$ solution (60 mL). The layers were separated, and the organic layer was washed with saturated $NaHCO_3$ (2×) and saturated NaCl solutions, dried with $MgSO_4$, and filtered. Evaporation of the solvent afforded the clean aldehyde as a yellow oil (0.11 g, 55% yield). ^{1}H NMR: δ = 9.70 (d, *J* = 2.4 Hz, 1 H), 3.86 (d, *J* = 5.4 Hz, 2 H), 2.34 (ttd, *J* = 7.0, 5.4, 2.4 Hz, 1 H), 1.72 (dquint., *J* = 14.5, 7.3 Hz, 1 H), 1.53 (dquint., *J* = 14.5, 7.2 Hz, 1 H), 0.94 (t, *J* = 7.5 Hz, 3 H), 0.87 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR: δ = 204.9, 61.7, 55.9, 25.9, 18.7, 18.3, 11.5, –5.4, –5.5 ppm. MS: *m*/*z* (%) = 217 (11) $[M + H]^+$, 201 (33), 159 (100), 84 (42), 71 (25). HRMS: calcd. for $C_{11}H_{25}O_2Si$ $[M + H]^+$ 217.1624; found 217.1575.

(2-Benzyl-3-oxopropoxy) *tert*-Butyldimethylsilane (19e): A solution of DMSO (1.86 mL, 26.2 mmol) in dry CH_2Cl_2 (6.5 mL) was added to a stirred solution of oxalyl chloride (1.0 mL, 11.8 mmol) in dry CH_2Cl_2 (28 mL) under an argon atmosphere and cooled to –60 °C.

After 10 min, a solution of alcohol **18′e** (3.0 g, 10.7 mmol) in dry CH_2Cl_2 (15 mL) was added, and the reaction mixture was stirred for 15 min at –60 °C. Et_3N (7.4 mL, 54.2 mmol) was added, and the cooling bath was removed, allowing the solution to reach room temperature, and the mixture was stirred for an additional 20 min. Water was added, and the aqueous phase was re-extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layer was washed successively with water, 0.5 M HCl solution (2×), water, and saturated NaCl solution. The organic layer was dried with $MgSO_4$, filtered, and concentrated to yield the product, which was further purified by chromatography (hexane/EtOAc, 3:1) to afford the clean aldehyde as a yellow oil (2.87 g, 97% yield). ^{1}H NMR: δ = 9.82 (d, J = 1.5 Hz, 1 H), 7.35–7.20 (m, 5 H), 3.93 (dd, J = 10.5, 4.2 Hz, 1 H), 3.78 (dd, J = 10.5, 5.4 Hz, 1 H), 3.09 (dd, J = 13.8, 6.0 Hz, 1 H), 2.86 (dd, J = 13.8, 8.1 Hz, 1 H), 2.72 (dtdd, J = 8.1, 5.9, 4.4, 1.5 Hz, 1 H), 0.94 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR: δ = 203.9, 139.0, 129.1, 128.6, 126.4, 60.8, 55.7, 31.3, 25.9, 18.3, –5.4 ppm. MS: m/z (%) = 279 (12) $[M + H]^+$, 278 (8) $[M]^+$, 277 (40), 221 (28), 191 (7), 145 (34), 117 (45), 105 (12), 91 (95). HRMS: calcd. for $C_{16}H_{26}O_2Si$ $[M]^+$ 278.1702; found 278.1647.

(2-Benzyl-3-diphenylselenoacetalpropoxy) *tert*-Butyldimethylsilane (20e): A solution of aldehyde **19e** (0.28 g, 1.0 mmol) in dry CCl_4 (0.5 mL) was slowly added under an argon atmosphere with stirring to a suspension of anhydrous zinc chloride (0.07 g, 0.5 mmol) in a solution of selenophenol (0.31 g, 2.0 mmol) in dry CCl_4 (1 mL). The reaction mixture was stirred at room temperature for 3.5 h and then diluted with diethyl ether (5 mL). The ether phase was washed with water and saturated NaCl solution, dried with $MgSO_4$, filtered, concentrated, and purified by chromatography (petroleum ether 40–60 °C) to give the clean selenoacetal (0.14 g, 24% yield). ^{1}H NMR: δ = 7.62–7.00 (m, 15 H), 4.84 (d, J = 2.7 Hz, 1 H), 3.81 (dd, J = 10.2, 7.2 Hz, 1 H), 3.68 (dd, J = 10.2, 4.8 Hz, 1 H), 3.11 (dd, J = 13.7, 6.0 Hz, 1 H), 2.63 (dd, J = 13.7, 8.4 Hz, 1 H), 2.25 (ddddd, J = 8.5, 6.9, 6.0, 4.8, 2.7 Hz, 1 H), 0.84 (s, 9 H), –0.04 (s, 3 H), –0.07 (s, 3 H) ppm. ^{13}C NMR: δ = 140.1, 133.7, 133.5, 129.2, 128.4, 127.7, 127.6, 126.2, 63.1, 48.4, 47.8 (d, J = 85.3 Hz), 35.5, 26.0, 18.3, –5.3, –5.4 ppm. MS: m/z (%) = 576 (4) $[M]^+$, 461 (2), 419 (5), 261 (100), 145 (51). HRMS: calcd. for $C_{28}H_{36}O^{80}Se_2Si$ $[M]^+$ 576.0866; found 576.0855.

2-Benzyl-3-(*tert*-butyldimethylsilyloxy)propylmethane Sulfonate (21e): A solution of alcohol **18′e** (1.2 g, 4.3 mmol) and Et_3N (0.9 mL, 6.4 mmol) in dry CH_2Cl_2 (7 mL) under an argon atmosphere was cooled to 0 °C. The solution was stirred for 30 min, followed by the slow addition (10 min) of MsCl (0.5 mL, 6.6 mmol) in dry CH_2Cl_2 (1.5 mL). Stirring was continued at 0 °C under an argon atmosphere for 3 h. The solution turned yellow. Ether was added, and the solution was washed with 1 N HCl and saturated $NaHCO_3$ and saturated NaCl solutions. The organic phase was dried with $MgSO_4$, filtered, and concentrated to give the clean product (1.51 g, 98% yield). ^{1}H NMR: δ = 7.31–7.16 (m, 5 H), 4.21 (dd, J = 9.6, 5.1 Hz, 1 H), 4.17 (dd, J = 9.6, 6 Hz, 1 H), 3.63 (dd, J = 10.2, 4.5 Hz, 1 H), 3.53 (dd, J = 10.2, 6 Hz, 1 H), 2.93 (s, 3 H), 2.70 (dd, J = 13.7, 7.8 Hz, 1 H), 2.64 (dd, J = 13.7, 7.2 Hz, 1 H), 2.16 (tquint., J = 7.5, 5.4 Hz, 1 H), 0.91 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR: δ = 138.9, 129.1, 128.5, 126.3, 69.4, 61.1, 42.7, 36.8, 33.5, 25.9, 18.2, –5.5 ppm. MS: m/z (%) = 359 (3) $[M + H]^+$, 263 (11), 153 (51), 131 (100), 91 (86). HRMS m/z for $C_{17}H_{31}O_4SiS$ $[M + H]^+$ 359.1712; found 359.1721.

2-Benzyl-3-(*tert*-butyldimethylsilyloxy)propyl (1-Phenyl-1*H*-tetrazol-5-yl) Sulfide ($22e_1$): 1-Phenyl-1*H*-tetrazol-5-thiol (2.46 g, 13.8 mmol) was dissolved in dry THF (29 mL). NaH (60% in mineral oil, 0.54 g) was added slowly, and the white suspension was stirred at room temperature for 15 min. A solution of mesylate **21e** (1.5 g, 4.2 mmol) in dry THF (6 mL) was added, and the mixture was stirred overnight at 50 °C. The mixture was cooled to room temperature, diluted with CH_2Cl_2 (30 mL), and washed with 10% NaOH solution (50 mL). The aqueous phase was re-extracted with CH_2Cl_2 (3 × 50 mL), and the volume of the combined organic phase was partially reduced to 50 mL under vacuum. The organic layer was washed with saturated NaCl solution, dried with $MgSO_4$, filtered, and concentrated to provide a yellow oil, which was chromatographed (hexane/EtOAc, 5:1) to give the clean product (1.34 g, 73% yield). ^{1}H NMR: δ = 7.59–7.50 (m, 5 H), 7.30–7.16 (m, 5 H), 3.64 (dd, J = 10.2, 3.9 Hz, 1 H), 3.52 (dd, J = 13.0, 6.4 Hz, 1 H), 3.50 (dd, J = 10.2, 4.5 Hz, 1 H), 3.47 (dd, J = 13.0, 6.8 Hz, 1 H), 2.78 (d, J = 7.2 Hz, 2 H), 2.30 (ttt, J = 7.8, 6.6, 4.3 Hz, 1 H), 0.90 (s, 9 H), 0.01 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR: δ = 154.7, 139.5, 133.9, 130.2, 129.9, 129.3, 128.5, 126.3, 124.0, 62.7, 42.3, 36.6, 35.3, 26.0, 18.3, –5.40, –5.44 ppm. MS: m/z (%) = 441 (76) $[M + H]^+$, 383 (61), 237 (46), 163 (25), 131 (36), 117 (24), 91 (100). HRMS: calcd. for $C_{23}H_{33}N_4OSiS$ $[M + H]^+$ 441.2144; found 441.2130.

2-Benzyl-3-(*tert*-butyldimethylsilyloxy)propyl (1-Phenyl-1*H*-tetrazol-5-yl) Sulfone ($23e_1$): *m*-CPBA (75%, 1.68 g, 9.7 mmol) was added to a stirred solution of sulfide $\mathbf{22e_1}$ (1.34 g, 3.0 mmol) in dry CH_2Cl_2 (24 mL) at 0 °C. The ice bath was removed, and the reaction mixture was allowed to proceed at room temperature overnight. CH_2Cl_2 (10 mL) was added, and the mixture was washed with saturated $Na_2S_2O_5$/10% NaOH solution (1:1, 30 mL). The layers were separated, and the aqueous phase was further extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with saturated $NaHCO_3$ and saturated NaCl solutions, dried with $MgSO_4$, filtered, and concentrated to give a yellow oil (1.43 g, 98% yield), which was crystallized (hexane/EtOAc, 3:1) to afford a white crystalline product. ^{1}H NMR: δ = 7.47–7.60 (m, 5 H), 7.13–7.28 (m, 5 H), 3.96 (dd, J = 14.9, 6.9 Hz, 1 H), 3.74 (dd, J = 10.2, 3.9 Hz, 1 H), 3.63 (dd, J = 14.9, 5.1 Hz, 1 H), 3.53 (dd, J = 10.2, 3.2 Hz, 1 H), 2.91 (dd, J = 13.5, 6.2 Hz, 1 H), 2.84 (dd, J = 13.5, 8.7 Hz, 1 H), 2.62 (dtq, J = 8.7, 6.6, 4 Hz, 1 H), 0.91 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR: δ = 153.8, 138.3, 133.0, 131.3, 129.6, 128.5, 126.6, 125.2, 62.0, 56.4, 37.5, 36.7, 25.9, 18.2, –5.6 ppm. MS: m/z (%) = 473 (3) $[M + H]^+$, 269 (11), 175 (35), 131 (54), 117 (96), 91 (100). HRMS: calcd. for $C_{23}H_{33}N_4O_3SiS$ $[M + H]^+$ 473.2043; found 473.2019.

2-Benzyl-3-(*tert*-butyldimethylsilyloxy)propyl Phenyl Sulfone (23e): Prepared from alcohol **14′e** according to the procedure described for **18e**. Yield: 84%. ^{1}H NMR: δ = 7.85 (d, J = 7.8 Hz, 2 H), 7.65 (t, J = 7.8 Hz, 1 H), 7.53 (t, J = 7.8 Hz, 2 H), 7.30–7.06 (m, 5 H), 3.65 (dd, J = 9.9, 4.2 Hz, 1 H), 3.50 (dd, J = 9.9, 4.2 Hz, 1 H), 3.37 (dd, J = 14.4, 6.6 Hz, 1 H), 3.01 (dd, J = 14.4, 5.1 Hz, 1 H), 2.80 (dd, J = 13.8, 6.6 Hz, 1 H), 2.76 (dd, J = 13.8, 7.5 Hz, 1 H), 2.33 (qq, J = 6.9, 4.8 Hz, 1 H), 0.89 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR: δ = 139.8, 138.8, 133.6, 129.3, 129.2, 128.5, 127.9, 126.4, 62.8, 56.2, 38.0, 36.9, 25.9, 18.2, –5.5 ppm. MS: m/z (%) = 405 (2) $[M + H]^+$, 347 (100), 131 (42), 91 (42). HRMS: calcd. for $C_{22}H_{33}O_3SiS$ $[M + H]^+$ 405.1920; found 405.1952.

2-(*tert*-Butyldimethylsilyloxy)methylbutyl (1-Phenyl-1*H*-tetrazol-5-yl) Sulfone ($23b_1$): Hydroxy sulfide $\mathbf{13'b_1}$ was silylated according to the procedure described for **18e**, followed by *m*-CPBA oxidation as described for **14**. Yield: 86% (overall). ^{1}H NMR: δ = 7.70–7.55 (m, 5 H), 3.98 (dd, J = 14.7, 6.5 Hz, 1 H), 3.79 (dd, J = 10.2, 4.2 Hz, 1 H), 3.65 (dd, J = 14.7, 5.1 Hz, 1 H), 3.65 (dd, J = 10.2, 4.4 Hz, 1 H), 2.24 (ttt, J = 6.5, 5.8, 4.4 Hz, 1 H), 1.61 (quint., 2 H), 0.94 (t, J = 7.4 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR: δ

= 154.1, 133.2, 131.5, 129.7, 125.2, 62.6, 56.8, 37.2, 25.9, 23.8, 18.3, 11.0, –5.5, –5.6 ppm. MS: *m*/*z* (%) = 411 (49) $[M + H]^+$, 353 (70), 325 (30), 265 (79), 175 (99), 145 (35), 117 (100). HRMS: calcd. for $C_{18}H_{31}N_4O_3SiS$ $[M + H]^+$ 411.1886; found 411.1859.

***trans*-Dipeptidyl Olefin Precursors 24:** LiHMDS (1 M in THF, 0.23 mL, 0.23 mmol) was slowly added to a stirring solution of sulfone **23** (0.23 mmol) in dry THF (1 mL) and HMPA (0.2 mL) under an argon atmosphere at –78 °C. After 20 min, a solution of *N*-trityl-alaninal (104 mg, 0.33 mmol) in dry THF (0.8 mL) was added slowly. After 3 h at –78 °C, the reaction mixture was further stirred at room temperature for 15 h. Ether (50 mL) and water (35 mL) were added, and the organic phase was washed with brine (30 mL), dried with $MgSO_4$, filtered, concentrated, and chromatographed (hexane/EtOAc, 19:1) to yield the clean product as a clear oil.

***N*-Trityl-5-amino-1-(*tert*-butyldimethylsilyloxy)-2-ethyl-3-hexene (24b):** Yield: 25 mg, 22%. ^{1}H NMR: δ = 7.55–7.11 (m, 15 H), 5.28 (dd, *J* = 15.6, 6.3 Hz, 1 H), 5.14 (dd, *J* = 15.6, 8.1 Hz, 1 H), 3.40 (dd, *J* = 9.8, 6.0 Hz, 1 H), 3.35 (dd, *J* = 9.8, 6.8 Hz, 1 H), 3.02 (br. quint., *J* = 6.3 Hz, 1 H), 1.90 (m, 1 H), 1.45 (m, 1 H), 1.10 (m, 1 H), 0.86 (s, 9 H), 0.80 (t, *J* = 7.5 Hz, 3 H), 0.59 (d, *J* = 6.0 Hz, 3 H), 0.00 (s, 6 H) ppm. ^{13}C NMR: δ = 147.2, 144.7, 137.5, 129.7, 129.2, 129.1, 128.4, 128.0, 127.8, 127.5, 126.9, 126.7, 126.3, 71.8, 66.7, 50.8, 46.7, 26.1, 24.0, 23.8, 18.5, 15.4, –5.2 ppm. MS: *m*/*z* (%) = 500 $[M + H]^+$, 484 (1), 422 (10), 258 (12), 243 (100). HRMS: calcd. for $C_{33}H_{46}NOSi$ $[M + H]^+$ 500.3349; found 500.3305.

***N*-Trityl-5-amino-2-benzyl-1-(*tert*-butyldimethylsilyloxy)-3-hexene (24e):** Yield: 40 mg, 31%. ^{1}H NMR: δ = 7.82–7.08 (m, 20 H), 5.28 (ddd, *J* = 15.8, 7.7, 0.9 Hz, 1 H), 5.13 (dd, *J* = 15.8, 6.2 Hz, 1 H), 3.40 (dd, *J* = 9.9, 5.4 Hz, 1 H), 3.35 (dd, *J* = 9.9, 6.3 Hz, 1 H), 2.97 (br. quint., *J* = 6.1 Hz, 1 H), 2.76 (dd, *J* = 13.5, 6.3 Hz, 1 H), 2.42 (dd, *J* = 13.5, 7.2 Hz), 2.27 (br. sext., *J* = 6.6 Hz, 1 H), 0.88 (s, 9 H), 0.57 (d, *J* = 6.0 Hz, 3 H), 0.06 (s, 6 H) ppm. ^{13}C NMR: δ = 147.0, 144.6, 140.6, 137.1, 125.6, 129.0, 128.3, 71.5, 65.3, 50.5, 46.1, 37.5, 25.9, 23.4, 18.3, –5.3, –5.4 ppm. HRMS: calcd. for $C_{38}H_{48}NOSi$ $[M + H]^+$ 562.3505; found 562.3519.

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