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Selective Formation of a *Z*-Trisubstituted Double Bond Using a 1-(*tert*-Butyl)tetrazolyl Sulfone

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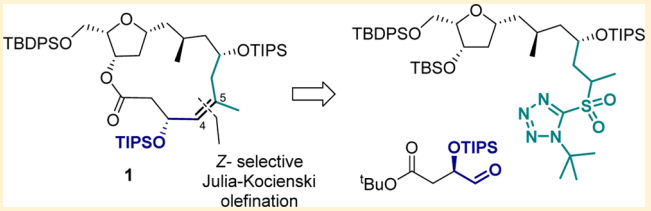
Supporting Information

ABSTRACT: In our effort to gain further insight into the enantioselective synthesis of the structural core of phormidolides B and C, we have discovered the formation of a *Z*-trisubstituted double bond. Here, we describe a highly selective process that can be applied to our target following a strategy that is based on Julia–Kocienski olefination. The use of 1-(*tert*-butyl)tetrazolyl sulfone affords the construction of the *Z*-trisubstituted alkene with high efficiency and stereoselectivity.



In the total synthesis of natural products, the design of efficient and stereoselective transformations is key to the success of a specific synthetic plan. Stereodefined alkenes are part of the structure of many natural products and serve as a foundation for a wide range of chemical transformations to introduce diversity into the carbon skeleton of a targeted compound. Among the synthetic tactics employed in the formation of C=C bonds, the most generally applicable are those involving olefination of carbonyl compounds, including the Wittig reaction,[1,2] and Horner–Wittig,[2,3] Horner–Wadsworth–Emmons,[2,4] Peterson,[5] Johnson,[6] Still–Gennari,[7] Julia–Lythgoe,[8a] and Julia–Kocienski[8b−d] olefinations. Other useful synthetic methods include alkenylation processes,[9] olefin metathesis,[10] and cycloaddition or sigmatropic reactions.[11] Nevertheless, despite the variety of available methods, the stereoselective formation of tri- and tetra-substituted double bonds is still a challenge for organic chemists.[12]

The lack of efficient, stereoselective methods to construct tri- and tetrasubstituted double bonds lies in the fact that congestion of starting materials makes it difficult for reagents to interact, and eclipsing interactions between substituents destabilizes both the products and the transition states leading to them. Moreover, the stereochemistry of the resulting products depends on a variety of parameters that are, in a majority of scenarios, difficult to control.

Modified Julia olefination has emerged as a useful tool for the construction of disubstituted alkenes in natural product synthesis[13] because of the easy preparation of starting materials, the mild reaction conditions needed, and the variety of tunable parameters that can control stereoselectivity. Nevertheless, only a few examples of stereoselective formation of tri- and tetrasubstituted double bonds using this methodology have been reported.[14,15] Some good results have been achieved with the use of 3,5-bis(trifluoromethyl)phenylsulfones[15a] and sulfoxides,[15b] but in the majority of cases, selectivity is directed toward the *E* isomer.[14−16] For Julia-type olefinations, a reliable method to attain the selective formation of *Z*-trisubstituted alkenes has not yet been well established, and its application to total synthesis to date reports only the selective formation of this motif by diastereomer separation.[17]

The use of 1-(*tert*-butyl)tetrazolyl sulfones for *Z*-selective olefinations was described in 2000 for the generation of disubstituted olefins.[18] Some work has been conducted on methylenation and cyclopropanation processes,[19] and on the preparation of fluorinated[20] and trifluoromethylated[21] alkenes, but its applicability for the total synthesis of natural products has been reported only in a few examples.[22]

In our work toward the synthesis of macrocyclic core **1**, which is common to phormidolides B and C,[23] we have discovered the formation of a *Z*-trisubstituted double bond, and our strategy depicts its formation by means of a Julia–Kocienski olefination (Figure 1). With this outlined background in mind, our strategy was to compare 1-(*tert*-butyl)tetrazolyl sulfone with the widely used 1-phenyltetrazolyl sulfone and assess its possible application to our total synthesis by proving its efficiency toward *Z*-selective formation of trisubstituted alkenes.

Here, we describe the optimization of the reaction conditions, the testing of two different sulfones (**2a** and **2b**),

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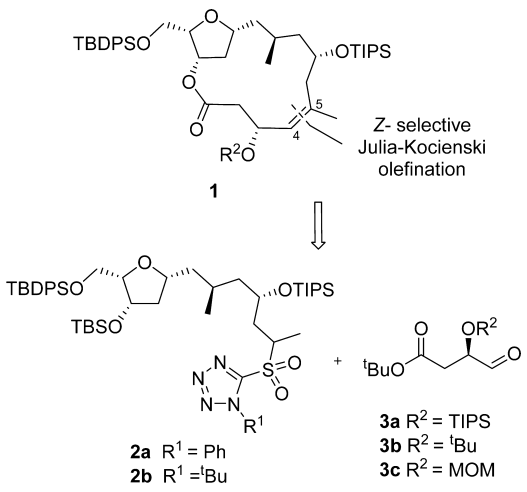
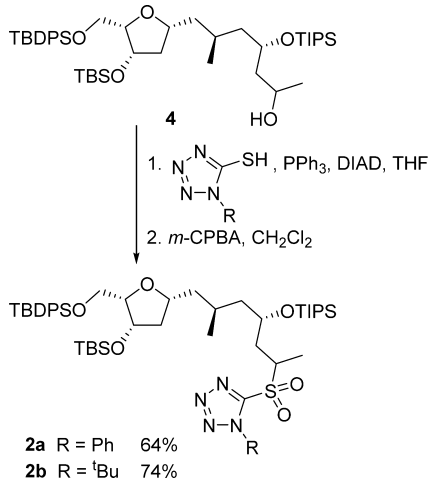


Figure 1. Retrosynthetic analysis of macrolactone **1**.

and the effect of steric bulk on the aldehyde partner (**3a**–**d**) by protection of the available α-hydroxyl, for this type of olefination.

Sulfones **2a** and **2b** were prepared starting from known alcohol **4**[24] by Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol or 1-(*tert*-butyl)-1*H*-tetrazole-5-thiol[25] and subsequent oxidation with 3-chloroperoxybenzoic acid (*m*-CPBA) (Scheme 1).

Scheme 1. Synthesis of Sulfones 2a,b



Enantioselective synthesis of aldehydes **3a**–**d** (Scheme 2) was performed by kinetic resolution of racemic β-hydroxy ester **5** with lipase PS-30, which produces ***R*-5** and ***S*-Ac-5** with excellent enantiopurity.[26] Aldehydes **3a**–**c** were prepared by protection of the free alcohol under mild conditions with triisopropylsilyl (TIPS), ^{t}Bu,[27] or methoxymethyl (MOM) ethers followed by reductive ozonolysis of the terminal olefins. Because we already had acetylated ***S*-Ac-5**, this enantiomer was directly subjected to reductive ozonolysis to give aldehyde **3d**.

Several strategies were tested for the formation of the double bond motif. Barbier conditions[28] did not provide good results, suggesting that premetalation of the sulfone was needed before the addition of the aldehyde. In our experience, the most appropriate base to perform olefinations has been lithium diisopropylamide (LDA). The use of BuLi, ^{t}BuLi, and KO^{t}Bu led to only decomposition of the starting materials. Potassium bis(trimethylsilyl)amide (KHMDS) afforded mainly elimination byproducts upon the formation of the α,β-unsaturated ester in product **6a**. Lithium bis(trimethylsilyl)amide (LiHMDS) gave yields lower than those with LDA, though it can also be used for olefinations.

We studied the optimal temperature using LDA as our base along with sulfone **2a** and aldehyde **3a** to obtain olefin **6a** as a model (Table 1).

Our experiments led to the conclusion that temperature had an effect on the diastereoselectivity of the reactions; lower temperatures favored *E* selectivity, whereas higher temperatures favored *Z* selectivity. Interestingly, when the reaction was performed at reflux temperature, the yield decreased dramatically, most likely due to decomposition of the starting materials. An intermediate temperature appeared to be the best option between yield and diastereoselectivity (Table 1, entry 2).

Reaction parameters were optimized at a fixed temperature (Table 2). The use of hexamethylphosphoramide (HMPA) as an additive increased the diastereoselectivity of the reactions toward the *Z* configuration (see entries 1, 2, 4, and 5). In general, the use of 1-phenyltetrazolyl sulfone led to the desired trisubstituted double bond with selectivities lower than those with 1-(*tert*-butyl)tetrazolyl sulfone (entries 2, 3, 5, and 6). The use of the 1-(*tert*-butyl)tetrazolyl sulfone afforded good to excellent *Z* selectivities with all of the tested aldehydes (entries 3, 6–8). Considering the effect of the steric bulk, lower *Z* selectivities were observed when a smaller protecting group was used (entries 7 and 8). The low yield observed for olefin **6d** (entry 8) may be due to the low stability of aldehyde **3d**, which can easily undergo an elimination process in the basic conditions of the reaction mixture.

The configuration of the double bonds formed was determined by NOESY experiments for **6a** and **6b** (Supporting Information). Irradiation of the vinyl proton at 5.30 and 5.24 ppm of ***Z*-6a** and ***Z*-6b**, respectively, produced a clear vinylic CH_3 singlet NOE signal at 1.67 and 1.65 ppm, respectively. On the other hand, for ***E*-6a** and ***E*-6b**, this effect was not observed when the vinyl proton was irradiated. However, the effect was observed when irradiation was performed at a signal of around 4.95 and 4.69 ppm, respectively, which corresponded to the C3 hydroxylated methyne hydrogen. Thus, the relative disposition of the methyl group of the double bond was determined in each case. In addition, the ^{13}C NMR chemical shift of the methyl group at C5 can be used as an indicator to deduce stereochemistry. Whereas the chemical shifts for alkenes ***E*-6a** and ***E*-6b** are 17.7 and 17.6 ppm, respectively, the chemical shifts for alkenes ***Z*-6a** and ***Z*-6b** are 23.1 and 23.2 ppm, respectively. The chemical shifts of the same signal for major alkenes **6c** and **6d** are 23.9 and 24.6 ppm, respectively, indicating that they have the *Z* configuration, which is consistent with our results. This fact may be explained by the effect that steric compression exerts on carbon nuclei, which causes a shielding effect.[29] In our case, the *E* diastereomer has the methyl residue in a more compressed state, and therefore, the ^{13}C NMR chemical shift is decreased. Thus, in our system, a chemical shift below 20 ppm by ^{13}C NMR suggests the formation of an *E* alkene, whereas a chemical shift over 20 ppm suggests the formation of a *Z* alkene.

The commonly accepted manifold mechanism of Julia–Kocienski olefination[30] describes the formation of either the *E* or the *Z* isomer based on the major species formed upon the addition of the sulfone to the aldehyde. In a chelating transition

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Scheme 2. Enantioselective Synthesis of Aldehydes 3a−d

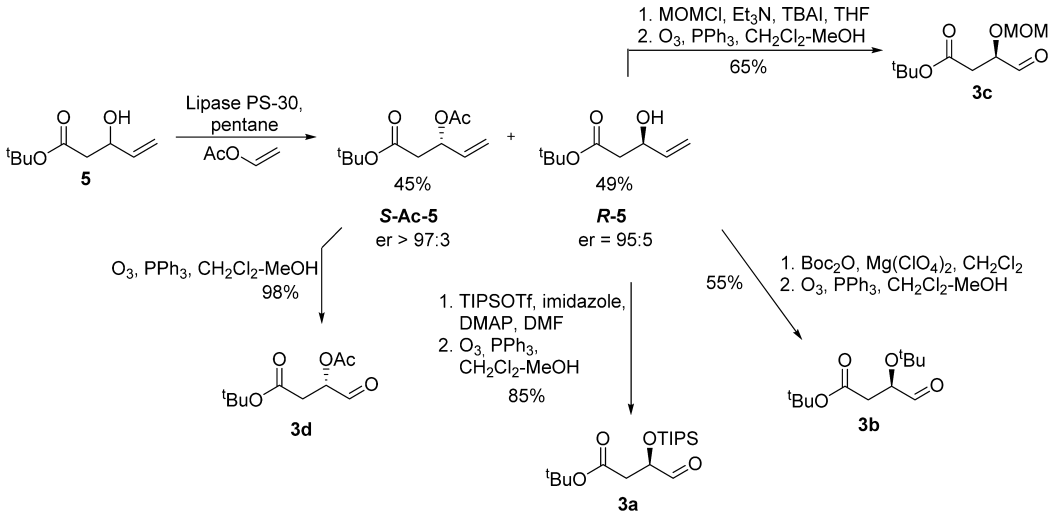
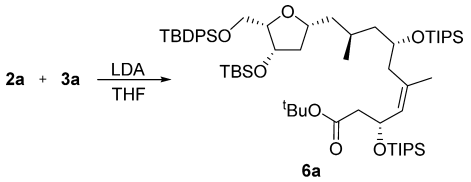


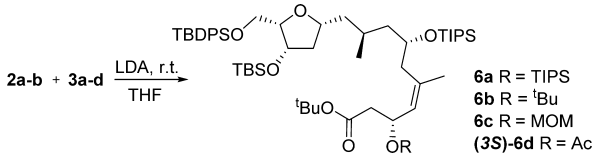
Table 1. Temperature Optimization



	T	yield	dr (E:Z)[a]
1	−78 °C	31%	62:38
2	rt	42%	35:65
3	66 °C	13%	30:70

[a]dr determined by ^{1}H NMR.

Table 2. Formation of *Z*-Trisubstituted Double Bonds



	sulfone	aldehyde	additive	product (yield)	dr (E:Z)[a]
1	**2a**	**3a**		**6a** (42%)	35:65
2	**2a**	**3a**	HMPA	**6a** (45%)	31:69
3	**2b**	**3a**	HMPA	**6a** (61%)	3:97
4	**2a**	**3b**		**6b** (30%)	50:50
5	**2a**	**3b**	HMPA	**6b** (42%)	33:67
6	**2b**	**3b**	HMPA	**6b** (47%)	3:97
7	**2b**	**3c**	HMPA	**6c** (59%)	12:88
8	**2b**	**3d**	HMPA	(**3S**)-**6d** (20%)	13:87

[a]dr determined by ^{1}H NMR.

state, the aldehyde approach would lead to a *cis*-disposed intermediate, which has the proper conformation for Smiles rearrangement. On the other hand, a less-constricted, open transition state would lead to the *trans* intermediate, which needs equilibration to the conformation that undergoes Smiles rearrangement. Next, antiperiplanar β elimination via extrusion of sulfur dioxide provides *Z* or *E* olefins from the original *cis* or *trans* intermediate, respectively (Figure 2).

It is postulated that aliphatic α-sulfonyl carbanions may exist in a conformation where the electron pair of the carbanion is in

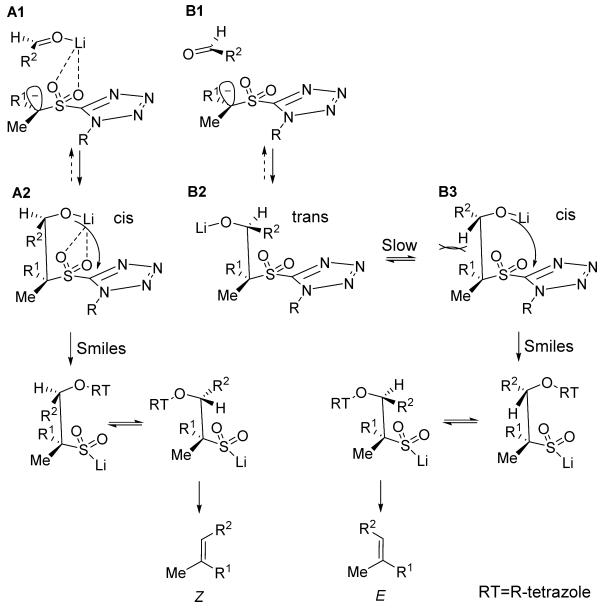


Figure 2. Putative structure of metallated tetrazolyl sulfones and a mechanistic explanation.

a gauche conformation relative to both oxygen atoms of the sulfone,[31] and this may be true for the aliphatic 1-phenyl- and 1-(*tert*-butyl)tetrazolyl sulfones as well.[8d] In our system, this fact may enable the simultaneous chelation of the aldehyde and the sulfone, minimizing the steric repulsion between R^1 and R^2 (Figure 2, **A1**). Addition through a chelated transition state may lead to conformation **A2**, and Smiles rearrangement followed by sulfur dioxide extrusion would explain the formation of the *Z* olefin (Figure 2). On the other hand, the conformation that results from an open-transition-state addition, and equilibrates to undergo Smiles rearrangement (Figure 2, **B3**), is extremely unfavored by the steric repulsions of substituents R^1 and R^2 and the extra steric bulk provided by the phenyl or *tert*-butyl group on the tetrazole. Thus, we postulate that pathway A is predominant.

This scenario explains why decreasing the steric bulk on the aldehyde, and the use of less bulky phenyl substituents on the tetrazole motif, leads to lower stereoselectivities. Moreover, the fact that at higher temperatures pathway A is predominant may

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be explained because conformation **A2** is more stable than **B3**, and the reaction is influenced by thermodynamic control. Nevertheless, at lower temperatures, the activation energy that leads to **B1** may be lower than the activation energy that leads to **A1** because the latter assumes a more constricted transition state, and a product resulting from kinetic control of the reaction is also observed. The addition of HMPA, which disrupts THF-lithium oligomers, favors the formation of the *Z* stereoisomer, but HMPA can also perform competitive chelation and favor *re* face addition, which would predictably lead to the *E* stereoisomer. Nevertheless, the role of chelating agents in the outcome of Julia-type olefinations is still not clear and may require further investigation.[32]

In summary, in our effort to attain the total synthesis of a natural product, we have encountered the formation of a *Z*-trisubstituted double bond, which, despite the variety of methods available, is still a difficult motif to afford in an efficient and stereoselective manner. We have described the optimization process toward our target and have provided a mechanistic explanation for our results. We have shown that the use of 1-(*tert*-butyl)tetrazolyl sulfone affords the construction of *Z*-trisubstituted alkenes with high efficiency while avoiding diasteromer separations, and we believe it is a step forward toward the applicability of this methodology. Our reactions were performed at room temperature in the presence of HMPA and premetallated before the addition of the aldehyde with a bulky protecting group on the α-hydroxyl. With this result, one of the most challenging points of the synthesis has been solved.

EXPERIMENTAL SECTION

General Procedure for the Preparation of Sulfones 2a and 2b. Diisopropyl azodicarboxylate (DIAD) (2.5 equiv) was added to an epimeric mixture solution of known alcohols **4** (A/B 65:35, 1 equiv), 1-phenyl-1*H*-tetrazole-5-thiol or 1-(*tert*-butyl)-1*H*-tetrazole-5-thiol[25] (2.5 or 1.4 equiv, respectively), and PPh_3 (2.5 equiv) in THF. The reaction mixture was stirred for 6 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography with hexane/Et_2O (95:5 to 80:20) to yield the corresponding thiotetrazole as a mixture of diastereomers.

A solution of 70% *m*-CPBA (1 equiv) and the above-mentioned thiotetrazole (2.3 equiv) in CH_2Cl_2 (50 mL) was stirred for 16 h. The reaction mixture was dissolved with saturated $Na_2S_2O_3$ and $NaHCO_3$, and the residue was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (95:5) yielded sulfone **2** as a mixture of diastereomers.

5-[(2RS,4S,6S)-7-((2R,4S,5S)-4-(tert-Butyldimethylsilyloxy)-5-(tert-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-yl-thio]-1-phenyl-1H-tetrazole. Alcohol **4** (1.60 g, 1.08 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (463 mg, 2.60 mmol) led to the title compound (A/B 65:35, 1.36 g, 70%). IR (KBr film) ν_{max}: 2930, 2864, 1598, 1500, 1462, 1388, 1251, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.05 (2s, $3H_{A+B}$); 0.00 and 0.01 (2s, $3H_{A+B}$); 0.79 and 0.80 (2s, $9H_{A+B}$); 0.86 (d, J = 6.0 Hz, $3H_A$); 0.91 (d, J = 6.0 Hz, $3H_B$); 1.01 (s, $13H_{A+B}$); 1.04, 1.05, and 1.06 (3s, $17H_{A+B}$); 1.35−1.45 (m, $2H_{A+B}$); 1.57 (d, J = 6.7 Hz, $3H_{A+B}$); 1.46−1.72 (m, $5H_{A+B}$); 1.87−2.02 (m, $1H_{A+B}$); 2.18−2.26 (m, $1H_{A+B}$); 3.72−3.79 (m, $2H_{A+B}$); 3.83−3.88 (m, $1H_{A+B}$); 3.89−3.96 (m, $1H_{A+B}$); 4.03−4.14 (m, $1H_{A+B}$); 4.15−4.24 (m, $1H_{A+B}$); 4.29−4.36 (m, $1H_{A+B}$); 7.31−7.42 (m, $6H_{A+B}$); 7.49−7.56 (m, $5H_{A+B}$); 7.66−7.72 (m, $4H_{A+B}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −5.2 (q_{A+B}), −4.7 (q_{A+B}), 12.9 (d_{A+B}), 17.7 (s_{A+B}), 17.9 (s_{A+B}), 18.2 ($2q_{A+B}$), 18.3 ($2q_{A+B}$), 19.2 (s_{A+B}), 19.8 (q_{A+B}), 19.9 (q_{A+B}), 21.7 (q_B), 23.2 (q_A), 25.7 (q_{A+B}), 26.9 (q_{A+B}), 27.4 ($2d_{A+B}$), 41.3 (d_A), 41.7 (d_B), 41.8 (t_{A+B}), 41.9 (t_{A+B}), 43.0 (t_{A+B}), 44.8 (t_A), 44.9 (t_B), 45.0 (t_B), 45.1 (t_A), 63.7 (t_{A+B}), 68.7 (d_A), 68.8 (d_B), 72.6 (d_{A+B}), 75.6 (d_A), 75.9 (d_B), 83.2 (d_B), 83.3 (d_A), 124.0 ($2d_{A+B}$), 127.5 ($2d_{A+B}$), 129.5 (d_{A+B}), 129.6 (d_{A+B}), 129.9 (d_{A+B}), 133.7 (s_{A+B}), 133.8 (s_{A+B}), 134.0 (s_{A+B}), 135.6 (d_{A+B}), 135.7 (d_{A+B}), 153.8 (s_B), 153.9 (s_A). HRMS (+ESI) m/z: [M + Na] calcd for $C_{51}H_{82}O_4N_4NaSSi_3$, 953.5257; found, 953.5240.

*5-[(2RS,4S,6S)-7-((2R,4S,5S)-4-(tert-Butyldimethylsilyloxy)-5-(tert-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-yl-sulfonyl]-1-phenyl-1H-tetrazole (**2a**).* The above-mentioned thiotetrazole (1.30 g, 1.40 mmol) led to sulfone **2a** (A/B 65:35, 1.22 g, 91%). IR (KBr film) ν_{max}: 2931, 2864, 1498, 1463, 1338, 1254, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.04 (2s, $3H_{A+B}$); 0.00 (2s, $3H_{A+B}$); 0.80 (s, $9H_{A+B}$); 0.88 and 0.90 (2d, J = 6.2 Hz, $3H_{A+B}$); 1.04, 1.06, and 1.07 (3s, $30H_{A+B}$); 1.35−1.70 and 1.81−1.89 (2m, $7H_{A+B}$); 1.49 (d, J = 6.9 Hz, $3H_A$); 1.55 (d, J = 6.8 Hz, $3H_B$); 2.08−2.25 and 2.42−2.50 (2m, $2H_{A+B}$); 3.70−3.78 (m, $2H_{A+B}$); 3.82−3.95 (m, $2H_{A+B}$); 4.05−4.31 (m, $2H_{A+B}$); 4.32−4.36 (m, $1H_{A+B}$); 7.30−7.42 (m, $6H_{A+B}$); 7.54−7.62 (m, $3H_{A+B}$); 7.64−7.70 (m, $6H_{A+B}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −5.2 (q_{A+B}), −4.2 (q_{A+B}), 12.9 (d_{A+B}), 13.5 (q_B), 16.1 (q_A), 18.0 (s_{A+B}), 18.2 ($4q_{A+B}$), 19.1 (q_B), 19.2 (s_{A+B}), 19.6 (q_A), 25.7 (q_{A+B}), 26.9 (q_{A+B}), 27.4 (d_A), 27.5 (d_B), 34.1 (t_B), 35.5 (t_A), 41.7 (t_B), 41.9 (t_A), 44.9 (t_A), 45.0 (t_{A+B}), 45.3 (t_B), 58.5 (d_A), 58.8 (d_B), 63.5 (t_{A+B}), 67.5 (d_B), 69.3 (d_A), 72.5 (d_{A+B}), 75.5 (d_A), 75.8 (d_B), 83.2 (d_B), 83.3 (d_A), 125.4 (d_{A+B}), 127.5 ($2d_{A+B}$), 129.5 ($4d_{A+B}$), 131.3 (d_{A+B}), 133.2 (s_{A+B}), 133.7 ($2s_{A+B}$), 134.0 ($2s_{A+B}$), 135.6 (d_{A+B}), 135.7 (d_{A+B}), 152.6 (s_B), 152.7 (s_A). HRMS (+ESI) m/z: [M + NH_4] calcd for $C_{51}H_{86}O_6N_5SSi_3$, 980.5601; found, 980.5587.

5-[(2RS,4S,6S)-7-((2R,4S,5S)-4-(tert-Butyldimethylsilyloxy)-5-(tert-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-yl-thio]-1-tert-butyl-1H-tetrazole. Alcohol **4** (490 mg, 0.63 mmol) and 1-(*tert*-butyl)-1*H*-tetrazole-5-thiol[2] (140 mg, 0.89 mmol) led to the title compound (A/B 65:35, 529 mg, 92%). IR (KBr film) ν_{max}: 2931, 2864, 1463, 1390, 1253, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.05 (s, $3H_B$); −0.04 (s, $3H_A$); −0.01 (s, $3H_B$); 0.01 (s, $3H_A$); 0.79 and 0.80 (2s, $9H_{A+B}$); 0.91 (2d, J = 6.2 Hz, $3H_{A+B}$); 1.03 (s, $10H_{A+B}$); 1.05, 1.06, and 1.07 (3s, $20H_{A+B}$); 1.36−1.48 (m, $3H_{A+B}$); 1.53 (d, J = 6.6 Hz, $3H_A$); 1.54 (d, J = 6.6 Hz, $3H_B$); 1.57−1.67 (m, $4H_{A+B}$); 1.68 and 1.70 (2s, $9H_{A+B}$); 1.84−2.02 (m, $1H_{A+B}$); 2.19−2.26 (m, $1H_{A+B}$); 3.72−3.80 (m, $2H_{A+B}$); 3.82−3.86 (m, $1H_{A+B}$); 3.87−3.96 (m, $1H_{A+B}$); 4.07−4.26 (m, $2H_{A+B}$); 4.30−4.36 (m, $1H_{A+B}$); 7.32−7.42 (m, $6H_{A+B}$); 7.67−7.72 (m, $4H_{A+B}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −5.2 (q_{A+B}), −4.7 (q_B), −4.6 (q_A), 12.9 ($2d_{A+B}$), 17.9 (s_{A+B}), 18.2 ($2q_{A+B}$), 18.3 ($2q_{A+B}$), 19.2 (s_{A+B}), 19.9 (q_{A+B}), 21.8 (q_B), 23.2 (q_A), 25.7 (q_{A+B}), 26.9 (q_{A+B}), 27.4 (d_{A+B}), 28.7 ($2q_{A+B}$), 41.7 (t_B), 41.8 (t_B), 41.9 (d_A), 42.3 (d_A), 43.1 (t_B), 43.2 (t_A), 44.9 (t_{A+B}), 45.1 (t_{A+B}), 60.8 (s_{A+B}), 63.7 (t_{A+B}), 68.8 (d_{A+B}), 72.6 (d_{A+B}), 75.6 (d_A), 75.9 (d_B), 83.2 (d_B), 83.3 (d_A), 127.5 ($2d_{A+B}$), 129.4 (d_{A+B}), 132.2 (s_{A+B}), 132.3(s_{A+B}), 133.7 (s_{A+B}), 134.0 (s_{A+B}), 135.6 (d_{A+B}), 135.7 (d_{A+B}), 152.1 (s_B), 152.2 (s_A). HRMS (+ESI) m/z: [M + H] calcd for $C_{49}H_{87}N_4O_4SSi_3$, 911.5750; found, 911.5740.

*5-[(2RS,4S,6S)-7-((2R,4S,5S)-4-(tert-Butyldimethylsilyloxy)-5-(tert-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl)-6-methyl-4-(triisopropylsilyloxy)heptan-2-yl-sulfonyl]-1-tert-butyl-1H-tetrazole (**2b**).* The above-mentioned thiotetrazole (2.56 g, 2.80 mmol) led to sulfone **2b** (A/B 65:35, 2.10 g, 80%). IR (KBr film) ν_{max}: 2941, 2865, 1463, 1332, 1158, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.04 (s, $3H_{A+B}$), 0.00 (2s, $3H_B$), 0.01 (2s, $3H_A$), 0.80 (2s, $9H_{A+B}$), 0.91 (d, J = 6.2 Hz, $3H_{A+B}$), 1.05 (2s, $9H_{A+B}$), 1.06 and 1.07 (2s, $21H_{A+B}$), 1.37−1.70 (m, $7H_{A+B}$), 1.50 (d, J = 6.9 Hz, $3H_A$), 1.56 (2d, J = 6.9 Hz, $3H_B$), 1.84 (s, $9H_{A+B}$), 2.12−2.26 and 2.42−2.49 (2m, $2H_{A+B}$), 3.71−3.78 (m, $2H_{A+B}$), 3.82−3.96 (m, $2H_{A+B}$), 4.07−4.16 and 4.24−4.43 (2m, $3H_{A+B}$), 7.32−7.42 (m, $6H_{A+B}$), 7.67−7.71 (m, $4H_{A+B}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −5.2 (q_{A+B}), −4.6 (q_{A+B}), 12.9 ($2d_{A+B}$), 13.9 (q_B), 16.3 (q_A), 18.0 (s_{A+B}), 18.2 ($2q_{A+B}$), 18.3 (q_{A+B}), 19.1 (q_B), 19.2 (s_{A+B}), 19.6 (q_A), 25.7 (q_{A+B}), 26.9 (q_{A+B}), 27.4 (d_A), 27.5 (d_B), 29.6 (q_{A+B}), 29.7 (q_{A+B}), 34.2 (t_B), 35.9 (t_A), 41.7 (t_B), 41.9 (t_A), 45.0 ($2t_A$), 45.2 (t_B), 45.3 (t_B), 58.8 (d_A), 59.3 (d_B), 63.5 (t_{A+B}), 65.3 (s_{A+B}), 67.6 (d_B), 69.5 (d_A), 72.5 ($2d_{A+B}$), 75.6 (d_A), 75.9 (d_B), 83.2 (d_B), 83.3 (d_A), 127.5 (d_{A+B}), 129.5 (d_{A+B}), 133.7 (s_{A+B}), 133.8 (s_{A+B}), 134.0 (s_{A+B}), 135.6 (d_{A+B}), 135.7 (d_{A+B}), 153.2 (s_B), 153.3 (s_A). HRMS (+ESI) m/z: [M + NH_4] calcd for $C_{49}H_{90}N_5O_6SSi_3$, 960.5914; found, 960.5907.

Kinetic Resolution of 5.[26] Lipase PS-30 (4.32 g) was added to a solution of racemic **5** (2.15 g, 12.50 mmol) in vinyl acetate (10 mL)

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and pentane (25 mL), and the suspension was stirred for 48 h at 37 °C. The residue was filtered through Celite 545, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (90:10) yielded ***R*-5** (1.05 g, 49%) and ***S*-Ac-5** (1.28 g, 48%) as colorless oils. ^{1}H NMR for ***R*-5** (400 MHz, $CDCl_3$): δ 1.46 (s, 9H), 2.43 (dd, J = 16.2, 8.3 Hz, 1H), 2.51 (dd, J = 16.2, 4.0 Hz, 1H), 3.11 (bs, OH), 4.45−4.52 (m, 1H), 5.14 (dt, J = 10.5, 1.4 Hz, 1H), 5.30 (dt, J = 17.2, 1.4 Hz, 1H), 5.87 (ddd, J = 17.2, 10.5, 5.5 Hz, 1H). ^{1}H NMR for ***S*-Ac-5** (400 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.05 (s, 3H), 2.52 (dd, J = 15.3, 5.8 Hz, 1H), 2.60 (dd, J = 15.3, 8.0 Hz, 1H), 5.20 (dd, J = 10.5, 1.0 Hz, 1H), 5.30 (dd, J = 17.2, 1.0 Hz, 1H), 5.57−5.63 (m, 1H), 5.83 (ddd, J = 17.2, 10.5, 6.2 Hz, 1H).

tert-Butyl-(R)-3-(triisopropylsilyloxy)pent-4-enoate. Triisopropylsilyl trifluoromethanesulfonate (1.98 mL, 7.34 mmol) was added to a solution of aldol ***R*-5** (1.05 g, 6.1 mmol), imidazole (830 mg, 12.20 mmol), and 4-dimethylaminopyridine (20 mg) in THF (60 mL), and the reaction mixture was stirred for 16 h at reflux temperature. The solvent was removed under reduced pressure, and the residue was dissolved in water and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (97:3) yielded the title compound (1.78 g, 89%) as a colorless oil. $[\alpha]_D$ − 3.8 (c 1.0, $CHCl_3$). IR (KBr film) ν_{max}: 2944, 2867, 1732, 1464, 1367, 1256, 1161 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04−1.07 (m, 21H), 1.43 (s, 9H), 2.37 (dd, J = 14.4, 7.5 Hz, 1H), 2.56 (dd, J = 14.4, 5.8 Hz, 1H), 4.59−4.65 (m, 1H), 5.06 (ddd, J = 10.4, 1.7, 1.1 Hz, 1H), 5.20 (ddd, J = 17.2, 1.7, 1.1 Hz, 1H), 5.87 (ddd, J = 17.2, 10.4, 6.7 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.3 (d), 18.0 (q), 18.1 (q), 28.1 (q), 45.2 (t), 71.3 (d), 80.4 (s), 114.5 (t), 140.6 (d), 170.1 (s). HRMS (+ESI) m/z: [M + H] calcd for $C_{18}H_{37}O_3Si$, 329.2507; found, 329.2506.

tert-Butyl-(R)-3-(tert-butoxy)pent-4-enoate. Di-*tert*-butyl dicarbonate (10.60 mL, 46.50 mmol) was added in portions to a mixture of aldol ***R*-5** (1.60 g, 9.30 mmol) and $Mg(ClO_4)_2$ (207 mg, 0.93 mmol) in CH_2Cl_2 (100 mL), and the reaction mixture was stirred for 16 h at reflux temperature. The resulting mixture was dissolved in water and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (96:4) yielded the title compound (1.33 g, 63%) as a colorless oil. $[\alpha]_D$ + 11.2 (c 1.0, $CHCl_3$). IR (KBr film) ν_{max}: 2977, 2933, 1732, 1367, 1159 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (s, 9H), 1.44 (s, 9H), 2.30 (dd, J = 14.5, 6.4 Hz, 1H), 2.43 (dd, J = 14.5, 7.4 Hz, 1H), 4.37−4.43 (m, 1H), 5.04 (ddd, J = 10.5, 1.6, 1.1 Hz, 1H), 5.20 (ddd, J = 17.3, 1.6, 1.1 Hz, 1H), 5.85 (ddd, J = 17.3, 10.5, 6.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 28.1 (q), 28.6 (q), 44.1 (t), 70.3 (d), 74.4 (s), 80.4 (s), 114.3 (t), 141.3 (d), 170.5 (s). HRMS (+ESI) m/z: [M + Na] calcd for $C_{13}H_{24}NaO_3$, 251.1618; found, 251.1618.

tert-Butyl-(R)-3-(methoxymethoxy)pent-4-enoate. Et_3N (2.62 mL, 18.80 mmol) was added to a solution of aldol ***R*-5** (540 mg, 3.10 mmol), MOMCl (0.71 mL, 9.4 mmol), and tetrabutylammonium iodide (347 mg, 0.9 mmol) in THF (20 mL), and the reaction mixture was stirred for 16 h at reflux temperature. The resulting mixture was dissolved in NH_4Cl and extracted with EtOAc, and the organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (90:10) yielded the title compound (494 mg, 73%) as a colorless oil. $[\alpha]_D$ + 64.3 (c 1.0, $CHCl_3$). IR (KBr film) ν_{max}: 2980, 1733, 1368, 1152 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.41 (dd, J = 15.0, 5.6 Hz, 1H), 2.55 (dd, J = 15.0, 8.1 Hz, 1H), 3.37 (s, 3H), 4.41−4.48 (m, 1H), 4.57 (d, J = 6.7 Hz, 1H), 4.69 (d, J = 6.7 Hz, 1H), 5.21 (ddd, J = 10.3, 1.6, 0.8 Hz, 1H), 5.29 (ddd, J = 17.2, 1.6, 1.0 Hz, 1H), 5.73 (ddd, J = 17.2, 10.3, 7.5 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 28.1 (q), 42.1 (t), 55.6 (q), 74.2 (d), 80.7 (s), 94.1 (t), 117.8 (t), 137.0 (d), 169.9 (s). HRMS (+ESI) m/z: [M + NH_4] calcd for $C_{11}H_{24}NO_4$, 234.1700; found, 234.1700.

General Procedure for Reductive Ozonolysis Reactions. Ozone gas was bubbled into a solution of the above-mentioned olefin (1 equiv) in a CH_2Cl_2/MeOH (4:1) mixture (100 mL) at −78 °C until a blue color persisted. Argon was then passed through the solution for 10 min at −78 °C to remove any excess ozone. Then, PPh_3 (1.3 equiv) was added, and the solution was stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure and filtered through silica with hexane/EtOAc (95:5) to yield the corresponding aldehyde **3** as a colorless oil.

*tert-Butyl-(R)-4-oxo-3-(triisopropylsilyloxy)butanoate (**3a**).* The above-mentioned TIPS-protected olefin (1.45 g, 4.41 mmol) led to aldehyde **3a** (1.35 g, 93%). $[\alpha]_D$ + 11.5 (c 1.0, $CHCl_3$). IR (KBr film) ν_{max}: 2944, 2868, 1736, 1464, 1367, 1256, 1157 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04−1.07 (m, 21H), 1.44 (s, 9H), 2.66 (ddd, J = 15.7, 5.8, 0.8 Hz, 1H), 2.78 (dd, J = 15.7, 4.0 Hz, 1H), 4.32 (ddd, J = 5.8, 4.0, 0.8 Hz, 1H), 9.80 (t, J = 0.8, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.1 (d), 17.8 (q), 28.0 (q), 41.22 (t), 74.2 (d), 81.4 (s), 169.0 (s), 204.2 (d). HRMS (+ESI) m/z: [M + H] calcd for $C_{17}H_{35}O_4Si$, 331.2299; found, 331.2297.

*tert-Butyl-(R)-4-oxo-3-(tert-butoxy)butanoate (**3b**).* The above-mentioned ^{t}Bu-protected olefin (1.30 g, 5.68 mmol) led to aldehyde **3b** (1.09 g, 83%). $[\alpha]_D$ + 45.9 (c 1.0, $CHCl_3$). IR (KBr film) ν_{max}: 2977, 1733, 1368, 1156 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (s, 9H), 1.44 (s, 9H), 2.52 (dd, J = 15.4, 5.7 Hz, 1H), 2.56 (dd, J = 15.4, 6.2 Hz, 1H), 4.18 (ddd, J = 6.2, 5.7, 1.5 Hz, 1H), 9.70 (d, J = 1.5, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 28.0 (q), 28.2 (q), 39.1 (t), 73.7 (d), 75.3 (s), 81.3 (s), 169.4 (s), 204.6 (d). HRMS (+ESI) m/z: [M + Na] calcd for $C_{12}H_{22}NaO_4$, 253.1410; found, 253.1412.

*tert-Butyl-(R)-4-oxo-3-(methoxymethoxy)butanoate (**3c**).* The above-mentioned MOM-protected olefin (460 mg, 2.13 mmol) led to aldehyde **3c** (418 mg, 90%). $[\alpha]_D$ + 10.8 (c 1.0, $CHCl_3$). IR (KBr film) ν_{max}: 2979, 1731, 1368, 1154 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.66 (dd, J = 16.3, 6.7 Hz, 1H), 2.73 (ddd, J = 16.3, 4.8, 0.4 Hz, 1H), 3.42 (s, 3H), 4.24 (ddd, J = 6.7, 4.8, 0.8 Hz, 1H), 4.76 (d, J = 6.9 Hz, 1H), 4.79 (d, J = 6.9 Hz, 1H), 9.76 (dd, J = 0.8, 0.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 28.0 (q), 37.5 (t), 56.0 (q), 79.0 (d), 81.6 (s), 97.2 (t), 169.1 (s), 201.8 (d). HRMS (+ESI) m/z: [M + H] calcd for $C_{10}H_{19}O_5$, 219.1227; found, 219.1230.

*tert-Butyl-(S)-3-acetoxy-4-oxobutanoate (**3d**).* Olefin ***S*-Ac-5** (1.00 g, 4.60 mmol) led to aldehyde **3d** (0.99 g, 98%). $[\alpha]_D$ − 15.0 (c 1.0, CH_2Cl_2). IR (KBr film) ν_{max}: 2980, 2935, 1733, 1370, 1158 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.16 (s, 3H), 2.78−2.81 (m, 2H), 5.24 (dd, J = 5.9, 5.4 Hz, 1H), 9.60 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.6 (q), 28.0 (q), 36.3 (t), 74.5 (d), 82.1 (s), 168.3 (s), 170.3 (s), 197.8 (d). HRMS (+ESI) m/z: [M + H] calcd for $C_{10}H_{17}O_5$, 217.1071; found, 217.076.

General Procedure for Julia−Kocienski Olefinations. A 2 M solution of LDA in THF/heptane/ethylbenzene (2 equiv) was added to a solution of sulfone **2** (1 equiv) and HMPA (2 equiv) in THF with 4 Å molecular sieves, and the solution was stirred for 1 min. After this time, a solution of aldehyde **3** (2 equiv) in THF was added, and the solution was stirred for an additional 2 h. After this time, saturated NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in EtOH and 40% $NaHSO_3$; the white precipitate was removed by filtration, and the solvent was concentrated under reduced pressure. Purification by silica gel column chromatography with hexane/Et_2O (97:3) yielded the corresponding olefin **6** as a colorless oil. For yields and diastereomeric ratios, please refer to Table 2.

*tert-Butyl-(3R,7S,9S,Z)-10-[(2R,4S,5S)-4-(tert-butyldimethylsilyloxy)-5-(tert-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl]-5,9-dimethyl-3,7-bis(triisopropylsilyloxy)dec-4-enoate (**Z-6a**).* $[\alpha]_D$ + 9.9 (c 1.3, CH_2Cl_2). IR (KBr film) ν_{max}: 2943, 2865, 1732, 1463, 1367, 1255, 1112 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.04 (s, 3H), 0.00 (s, 3H), 0.80 (s, 9H), 0.93 (d, J = 6.4 Hz, 3H), 1.04 and 1.06 (2bs, 51H), 1.28−1.34 (m, 1H), 1.42 (s, 9H), 1.43−1.58 (m, 4H), 1.63−1.66 (m, 1H), 1.67 (s, 3H), 2.12−2.26 (m, 3H), 2.34−2.42 (m, 2H), 3.72−3.79 (m, 2H), 3.82−3.89 (m, 2H), 4.05−4.14 (m, 1H), 4.30−4.36 (m, 1H), 4.93−4.98 (m, 1H), 5.30 (d, J = 7.6 Hz, 1H), 7.33−7.43 (m, 6H), 7.64−7.73 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −5.2 (q), −4.6 (q), 12.5 (d), 13.0 (d), 17.9 (s), 18.1 (q), 18.2 (q), 18.3 (2q), 19.2 (s), 20.5 (q), 23.1 (q), 25.7 (q), 26.9 (q), 27.9 (d), 28.1 (q),

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40.6 (t), 42.2 (t), 44.0 (t), 45.7 (t), 46.1 (t), 63.6 (t), 67.0 (d), 68.8 (d), 72.5 (d), 76.3 (d), 79.9 (s), 83.2 (d), 127.5 (2d), 129.5 (2d), 131.9 (d), 133.7 (s), 133.4 (s), 134.0 (s), 135.6 (d), 135.7 (d), 170.4 (s). HRMS (+ESI) m/z: [M + NH_4] calcd for $C_{61}H_{114}NO_7Si_4$, 1084.7667; found, 1084.7654.

*tert-Butyl-(3R,7S,9S,E)-10-[(2R,4S,5S)-4-(tert-butyldimethylsilyloxy)-5-(tert-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl]-5,9-dimethyl-3,7-bis(triisopropylsilyloxy)dec-4-enoate (**E-6a**).* IR (KBr film) ν_{max}: 2943, 2865, 1732, 1463, 1367, 1255, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.06 (s, 3H), −0.01 (s, 3H), 0.79 (s, 9H), 0.93 (d, J = 6.7 Hz, 3H), 1.03 and 1.06 (2bs, 51H), 1.19−1.28 (m, 1H), 1.42 (s, 9H), 1.44−1.56 (m, 4H), 1.65 (s, 3H), 1.68−1.76 (m, 1H), 2.11−2.25 (m, 3H), 2.27 (dd, J = 14.5, 5.6 Hz, 1H), 2.47 (dd, J = 14.5, 7.0 Hz, 1H), 3.72−3.79 (m, 2H), 3.81−3.89 (m, 2H), 3.99−4.07 (m, 1H), 4.32 (dt, J = 6.3, 4.1 Hz, 1H), 4.91 (ddd, J = 8.7, 7.0, 5.6 Hz, 1H), 5.25 (d, J = 8.7 Hz, 1H), 7.32−7.43 (m, 6H), 7.66−7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −5.2 (q), −4.7 (q), 12.4 (d), 12.9 (d), 17.7 (q), 20.0 (s), 18.0 (q), 18.1 (q), 18.3 (q), 19.2 (s), 20.9 (q), 25.7 (q), 26.9 (q), 27.7 (d), 28.1 (q), 42.3 (t), 43.7 (t), 44.7 (t), 45.4 (t), 47.7 (t), 63.7 (t), 66.9 (d), 69.8 (d), 72.6 (d), 76.5 (d), 80.1 (s), 83.2 (d), 127.5 (d), 129.4 (d), 131.1 (d), 133.6 (s), 133.8 (s), 134.1 (s), 135.6 (d), 135.7 (d), 170.3 (s). HRMS (+ESI) m/z: [M + NH_4] calcd for $C_{61}H_{114}NO_7Si_4$, 1084.7667; found, 1084.7654.

*tert-Butyl-(3R,7S,9S,Z)-3-(tert-butoxy)-10-[(2R,4S,5S)-4-(tert-butyldimethylsilyloxy)-5-(tert-butyldiphenylsilyloxymethyl)-tetrahydrofuran-2-yl]-5,9-dimethyl-7-(triisopropylsilyloxy)dec-4-enoate (**Z-6b**).* $[\alpha]_D$ + 5.2 (c 1.0, $CHCl_3$). IR (KBr film) ν_{max}: 2931, 2864, 1732, 1463, 1365, 1256, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.05 (s, 3H), 0.00 (s, 3H), 0.80 (s, 9H), 0.95 (d, J = 6.4 Hz, 3H), 1.04 (bs, 21H), 1.05 (s, 9H), 1.15 (s, 9H), 1.30−1.39 (m, 1H), 1.44 (s, 9H), 1.46−1.63 (m, 3H), 1.64−1.70 (m, 1H), 1.65 (s, 3H), 2.16−2.28 (m, 4H), 2.30−2.34 (m, 2H), 3.72−3.79 (m, 2H), 3.82−3.92 (m, 2H), 4.07−4.16 (m, 1H), 4.33 (dt, J = 6.4, 4.1 Hz, 1H), 4.64−4.72 (m, 1H), 5.24 (d, J = 6.8 Hz, 1H), 7.32−7.43 (m, 6H), 7.66−7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −5.2 (q), −4.7 (q), 13.0 (d), 18.0 (s), 18.2 (q), 18.3 (q), 19.2 (s), 20.4 (q), 23.2 (q), 25.7 (q), 26.9 (q), 28.0 (d), 28.1 (q), 28.9 (q), 40.5 (t), 42.1 (t), 44.2 (t), 44.3 (t), 46.3 (t), 63.7 (t), 66.6 (d), 68.9 (d), 72.6 (d), 73.7 (s), 76.3 (d), 79.8 (s), 83.2 (d), 127.5 (2d), 129.4 (d), 131.4 (s), 132.5 (d), 133.8 (s), 134.0 (s), 135.6 (d), 135.7 (d), 170.6 (s). HRMS (+ESI) m/z: [M + Na] calcd for $C_{56}H_{98}NaO_7Si_3$, 989.6513; found, 989.6517.

*tert-Butyl-(3R,7S,9S,E)-3-(tert-butoxy)-10-[(2R,4S,5S)-4-(tert-butyldimethylsilyloxy)-5-(tert-butyldiphenylsilyloxymethyl)-tetrahydrofuran-2-yl]-5,9-dimethyl-7-(triisopropylsilyloxy)dec-4-enoate (**E-6b**).* IR (KBr film) ν_{max}: 2931, 2864, 1732, 1463, 1365, 1256, 1113 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.06 (s, 3H), −0.01 (s, 3H), 0.79 (s, 9H), 0.92 (d, J = 6.6 Hz, 3H), 1.05 (bs, 30H), 1.15 (s, 9H), 1.20−1.28 (m, 1H), 1.44 (s, 9H), 1.45−1.68 (m, 3H), 1.63−1.68 (m, 1H), 1.69 (s, 3H), 2.09−2.26 (m, 5H), 2.38 (dd, J = 14.4, 8.8 Hz, 1H), 3.72−3.78 (m, 2H), 3.81−3.89 (m, 2H), 3.99−4.05 (m, 1H), 4.32 (dt, J = 6.2, 4.2 Hz, 1H), 4.64 (td, J = 8.8, 4.7 Hz, 1H), 5.20 (d, J = 8.8 Hz, 1H), 7.32−7.42 (m, 6H), 7.67−7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −5.2 (q), −4.7 (q), 12.9 (d), 17.6 (q), 18.0 (s), 18.3 (2q), 19.2 (s), 20.8 (q), 25.7 (q), 26.9 (q), 27.7 (d), 28.2 (q), 28.8 (q), 42.3 (t), 43.9 (2t), 44.8 (t), 47.4 (t), 63.8 (t), 66.5 (d), 70.0 (d), 72.6 (d), 73.7 (s), 76.4 (d), 80.1 (s), 83.1 (d), 127.5 (2d), 129.4 (2d), 131.7 (d), 131.8 (s), 133.8 (s), 135.6 (d), 135.7 (d), 170.6 (s). HRMS (+ESI) m/z: [M + Na] calcd for $C_{56}H_{98}NaO_7Si_3$, 989.6513; found, 989.6517.

*tert-Butyl-(3R,7S,9S,Z)-10-[(2R,4S,5S)-4-(tert-butyldimethylsilyloxy)-5-(tert-butyldiphenylsilyloxymethyl)tetrahydrofuran-2-yl]-3-(methoxymethoxy)-5,9-dimethyl-7-(triisopropylsilyloxy)dec-4-enoate (**Z-6c**).* $[\alpha]_D$ + 22.2 (c 1.0, $CHCl_3$). IR (KBr film) ν_{max}: 2930, 2863, 1730, 1462, 1367, 1255, 1151 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.05 (s, 3H), 0.00 (s, 3H), 0.80 (s, 9H), 0.94 (d, J = 6.3 Hz, 3H), 1.05 (2bs, 30H), 1.31−1.41 (m, 1H), 1.44 (s, 9H), 1.45−1.68 (m, 5H), 1.73 (d, J = 1.4 Hz, 3H), 2.19−2.28 (m, 3H), 2.39 (dd, J = 15.0, 4.6 Hz, 1H), 2.45 (dd, J = 15.0, 8.7 Hz, 1H), 3.33 (s, 3H), 3.72−3.78 (m, 2H), 3.82−3.90 (m, 2H), 4.06−4.14 (m, 1H), 4.33 (dt, J = 6.2, 4.0 Hz, 1H), 4.48 (d, J = 6.7 Hz, 1H), 4.65 (d, J = 6.7 Hz, 1H), 4.73−4.80 (m, 1H), 5.11 (d, J = 9.2 Hz, 1H), 7.32−7.43 (m, 6H), 7.66−7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −5.2 (q), −4.6 (q), 13.0 (d), 18.0 (s), 18.3 (2q), 19.2 (s), 20.1 (q), 23.9 (q), 25.7 (q), 26.9 (q), 27.9 (d), 28.1 (q), 40.2 (t), 42.2 (t), 42.6 (t), 44.3 (t), 45.8 (t), 55.4 (q), 63.6 (t), 69.0 (d), 69.1 (d), 72.6 (d), 76.2 (d), 80.2 (s), 83.2 (d), 93.5 (t), 126.7 (d), 127.5 (2d), 129.4 (d), 133.8 (s), 134.0 (s), 135.6 (d), 135.7 (d), 137.9 (s), 170.2 (s). HRMS (+ESI) m/z: [M + NH_4] calcd for $C_{54}H_{98}NO_8Si_3$, 972.6595; found, 972.6586.

*tert-Butyl-(3S,7S,9S,Z)-3-acetoxy-10-[(2R,4S,5S)-4-(tert-butyldimethylsilyloxy)-5-(tert-butyldiphenylsilyloxymethyl)-tetrahydrofuran-2-yl]-5,9-dimethyl-7-(triisopropylsilyloxy)dec-4-enoate (**Z-6d**).* $[\alpha]_D$ + 11.0 (c 1.0, $CHCl_3$). IR (KBr film) ν_{max}: 2931, 2864, 1739, 1463, 1368, 1251, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.05 (s, 3H), 0.00 (s, 3H), 0.80 (s, 9H), 0.95 (d, J = 6.6 Hz, 3H), 1.05 (2bs, 30H), 1.28−1.39 (m, 2H), 1.42 (s, 9H), 1.45−1.61 (m, 3H), 1.66−1.72 (m, 1H), 1.73 (d, J = 1.4 Hz, 3H), 1.98 (s, 3H), 2.12−2.27 (m, 2H), 2.42 (dd, J = 15.1, 4.4 Hz, 1H), 2.54 (dd, J = 15.1, 9.0 Hz, 1H), 2.64 (dd, J = 13.6, 6.7 Hz, 1H), 3.71−3.78 (m, 2H), 3.82−3.90 (m, 2H), 4.03−4.11 (m, 1H), 4.29−4.35 (m, 1H), 5.18 (d, J = 9.0 Hz, 1H), 5.83 (td, J = 9.0, 4.4 Hz, 1H), 7.32−7.43 (m, 6H), 7.67−7.72 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −5.2 (q), −4.6 (q), 13.0 (d), 18.0 (s), 18.3 (q), 19.2 (s), 20.5 (q), 21.1 (q), 24.6 (q), 25.7 (q), 26.9 (q), 27.8 (d), 28.0 (q), 40.6 (t), 41.5 (t), 42.2 (t), 44.0 (t), 47.0 (t), 63.6 (t), 67.7 (d), 69.9 (d), 72.6 (d), 76.2 (d), 80.7 (s), 83.2 (d), 124.2 (d), 127.5 (d), 129.4 (d), 133.8 (s), 135.6 (d), 135.7 (d), 169.1 (s), 169.7 (s). HRMS (+ESI) m/z: [M + NH_4] calcd for $C_{54}H_{96}NO_8Si_3$, 970.6438; found, 970.6429.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General procedures and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44−57. (b) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318−1330.

(2) Gu, Y.; Tian, S.-K. *Top. Curr. Chem.* **2012**, 197−238.

(3) (a) Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61−63. (b) Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499−2505.

(4) (a) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733−1738. (b) Wadsworth, W. S. *Org. React.* **1977**, *25*, 73−253.

(5) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780−784. (b) van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195−200.

(6) Johnson, C. R.; Shanklin, J. R.; Kirchhoff, R. A. *J. Am. Chem. Soc.* **1973**, *95*, 6462−6463.

(7) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.

(8) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833−4836. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175−1178. (c) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563−2585. (d) Aïssa, C. *Eur. J. Org. Chem.* **2009**, 1831−1844.

(9) (a) Cross Coupling and Heck-Type Reactions. In *Science of Synthesis*; Molander, G. A., Wolfe, J. P., Larhed, M., Eds.; Thieme Medical Publishers: New York, 2013. (b) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841−870. (c) Negishi, E.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474−1485.
(10) (a) Grubbs, R. H. *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003. (b) Fürstner, A. *Science* **2010**, *341*, 1377−1364. (c) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746−1787.
(11) (a) Jørgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698.
(12) Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698−4745.
(13) Chatterjee, B.; Bera, S.; Mondal, D. *Tetrahedron: Asymmetry* **2014**, *25*, 1−55.
(14) Savolainen, M. A.; Wu, J. *Org. Lett.* **2013**, *15*, 3802−3804.
(15) (a) Alonso, D. A.; Fuensanta, M.; Nájera, C. *Eur. J. Org. Chem.* **2006**, 4747−4754. (b) Pospíšil, J.; Pospíšil, T.; Markó, I. *Org. Lett.* **2005**, *7*, 2373−2376.
(16) Robiette, R.; Pospíšil, J. *Eur. J. Org. Chem.* **2013**, 836−840.
(17) (a) Fujiwara, N.; Kinoshita, M.; Hiroyuki, A. *Tetrahedron: Asymmetry* **2006**, *17*, 3037−3045. (b) Takamura, H.; Murata, T.; Asai, T.; Kadota, I.; Uemura, D. *J. Org. Chem.* **2009**, *74*, 6658−6666. (c) Lorente, A.; Pla, D.; Cañedo, L. M.; Albericio, F.; Álvarez, M. *J. Org. Chem.* **2010**, *75*, 8505−8515. (d) Ishigai, K.; Fuwa, H.; Hashizume, K.; Fukazawa, R.; Cho, Y.; Yotsu-Yamashita, M.; Sasaki, M. *Chem.—Eur. J.* **2013**, *19*, 5276−5288. (e) Ding, X.-B.; Furkert, D. P.; Capon, R. J.; Brimble, M. A. *Org. Lett.* **2014**, *16*, 378−381.
(18) Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 365−366.
(19) (a) Aïssa, C. *J. Org. Chem.* **2006**, *71*, 360−363. (b) Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306−6307.
(20) Zhu, L.; Ni, C.; Zhao, Y.; Hu, J. *Tetrahedron* **2010**, *66*, 5089−5100.
(21) Ayeni, D. O.; Mandal, S. K.; Zajc, B. *Tetrahedron Lett.* **2013**, *54*, 6008−6011.
(22) (a) van Summeren, R. P.; Moody, D. B.; Feringa, B. L.; Minnaard, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 4546−4547. (b) Werneburg, M.; Hertweck, C. *ChemBioChem* **2008**, *9*, 2064−2066. (c) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632−16633. (d) Buter, J.; Yeh, E. A.-H.; Budavich, O. W.; Damodaran, K.; Minnaard, A. J.; Curran, D. P. *J. Org. Chem.* **2013**, *78*, 4913−4918.
(23) Lorente, A.; Gil, A.; Fernández, R.; Cuevas, C.; Albericio, F.; Álvarez, M. *Chem.—Eur. J.* Accepted.
(24) The epimeric mixture of alcohols is used because this stereocenter is lost when the α-sulfonyl anion is formed.
(25) Quast, H.; Bieber, L. *Chem. Ber.* **1981**, *114*, 3253−3272.
(26) Vrielynck, S.; Vandewalle, M. *Tetrahedron Lett.* **1995**, *36*, 9023−9026.
(27) Bartoli, G.; Bosco, M.; Locatelli, M.; Marcatoni, E.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2005**, *7*, 427−430.
(28) A 2 M solution of LDA in THF/heptane/ethylbenzene (2 equiv) was added to a solution of sulfone (1 equiv) and aldehyde (2 equiv) in THF with 4 Å molecular sieves, and the solution was stirred for 2 h. After this time, saturated NH_4Cl was added, the residue was extracted with CH_2Cl_2, and the solvent was removed under reduced pressure.
(29) Seidl, P. R.; Leal, K. Z.; Uberti Costa, V. E.; Stapelbroek Mollmann, M. E. *Magn. Reson. Chem.* **1998**, *36*, 261−266.
(30) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856−878.
(31) Gais, H.-J.; Müller, J.; Vollhardt, J.; Lindner, H. J. *J. Am. Chem. Soc.* **1991**, *113*, 4002−4003.
(32) Pospíšil, J. *Tetrahedron Lett.* **2011**, *52*, 2348−2352.