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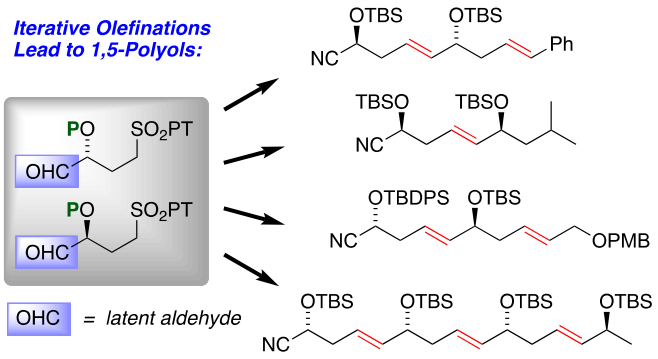
Unified Strategy for 1,5,9- and 1,5,7-Triols via Configuration-Encoded 1,5-Polyol Synthesis: Enantioselective Preparation of γ-Sulfonyl-α-silyloxyaldehydes and Iterative Julia–Kocienski Coupling

Ryan M. Friedrich‡, Gopeekrishnan Sreenilayam†, Jacob Hackbarth, and Gregory K. Friestad*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242 USA

email: gregory-friestad@uiowa.edu



Abstract: Diverse classes of natural products contain chiral 1,5-polyols, within which may be stereochemical triads of 1,5,9- and 1,5,7-triols. Biological activities associated with compounds containing these motifs warrant targeted synthetic strategies to access all stereoisomers of a 1,5-polyol family from cheap and easily accessible reagents while avoiding the need to determine configurations at each alcohol stereocenter. Here we address these problems via design and implementation of an iterative configuration-encoded strategy to access 1,5-polyols with unambiguous stereocontrol; the coupling event exploits Julia–Kocienski reactions of enantiopure α-silyloxy-γ-sulfononitriles. These building blocks, bearing sulfone at one terminus and α-silyloxyaldehyde (in latent form) at the other, were prepared via

‡ Current Address: Department of Genetics and Genome Sciences, Small-Molecule Drug Development Core, Case Western Reserve University
† Current Address: Department of Chemistry, Valdosta State University

asymmetric catalysis. An efficient scalable route to these building blocks was developed, leading to enantiopure samples in multigram quantities. Preliminary studies of acetals as the latent aldehyde functionality in the α-silyloxyaldehyde showed that Julia–Kocienski coupling of these building blocks was effective, but iterative application was thwarted during acetal hydrolysis, leading to use of nitrile to perform the latent aldehyde function. A variety of 1,5-polyols, including a 1,5,9,13-tetraol and a differentially protected 1,5,9-triol were prepared, validating the approach. The accompanying paper describes the application of this configuration-encoded 1,5-polyol synthesis to 1,5,9- and 1,5,7-triols found in tetrafibricin.

1. Introduction

Naturally occuring compounds bearing 1,5-polyol structures present bioactivities of potential utility in drug discovery; representative examples (Figure 1) include tetrafibricin[1] (antithrombotic) and muricapentocin[2] (anticancer). Further illustrating the breadth in association of biological activities with 1,5-polyols are lydicamycin[3] (antibiotic active against multidrug resistant strains), sporminarin B[4] (antifungal), and amphidinol 3[5] (hemolytic and antifungal). Despite their common occurence in biologically active compounds, there are only a handful of published methodologies addressing the synthesis and stereochemical assignment of chiral 1,5-polyols.[6] Strategies for the construction and characterization of 1,3-polyols have been well documented,[7] however, few are easily adaptable to 1,5-polyols. Applying biomimetic polyketide and other aldol-based methodologies used for the synthesis of 1,3-polyols would require selective dehydration after assembly, a prospect fraught with challenges of regioselectivity and stereoselectivity. Additionally, the isolated hydroxyl stereocenters of 1,5-diols make relative and absolute configuration assignments nontrivial.[8] As with muricapentocin (Figure 1), this analytical obstacle results in natural products isolation disclosures lacking complete stereostructures; it also impedes any synthetic chemist seeking secure configurational assignments *en route* to natural products of this class.

The variety of structures found in 1,5-polyols includes *syn*- and *anti*-diastereromerism, saturation or unsaturation, and *E*/*Z* olefin isomers. Selected hydroxyl groups may be engaged in macrolactone ester linkages. Notably, a 1,5-diol may be flanked by 1,3-diols in a 1,5,7-triol stereotriad. Thus, we sought a unified approach to preparing all stereoisomeric 1,5-polyols, as well as the variants just mentioned. A guiding inspiration was provided by tetrafibricin, which contains both 1,5,9-triol and 1,5,7-triol motifs (Figure 1).

In the last few years, several strategies have emerged to specifically target the chiral 1,5-diols present in tetrafibricin and related targets.[9,10,11,12,13,14,15,16,17,18,19] Some limitations and disadvantages inherent to the prior art include the use of cumbersome reaction conditions (e.g. toxic metals or high pressures), expensive chiral reagents used in stoichiometric quantities, and different reagents required for different stereoisomers. In many cases, assigning the new configuration of each remotely generated alcohol stereogenic center also adds extra steps to the workflow.

Figure 1

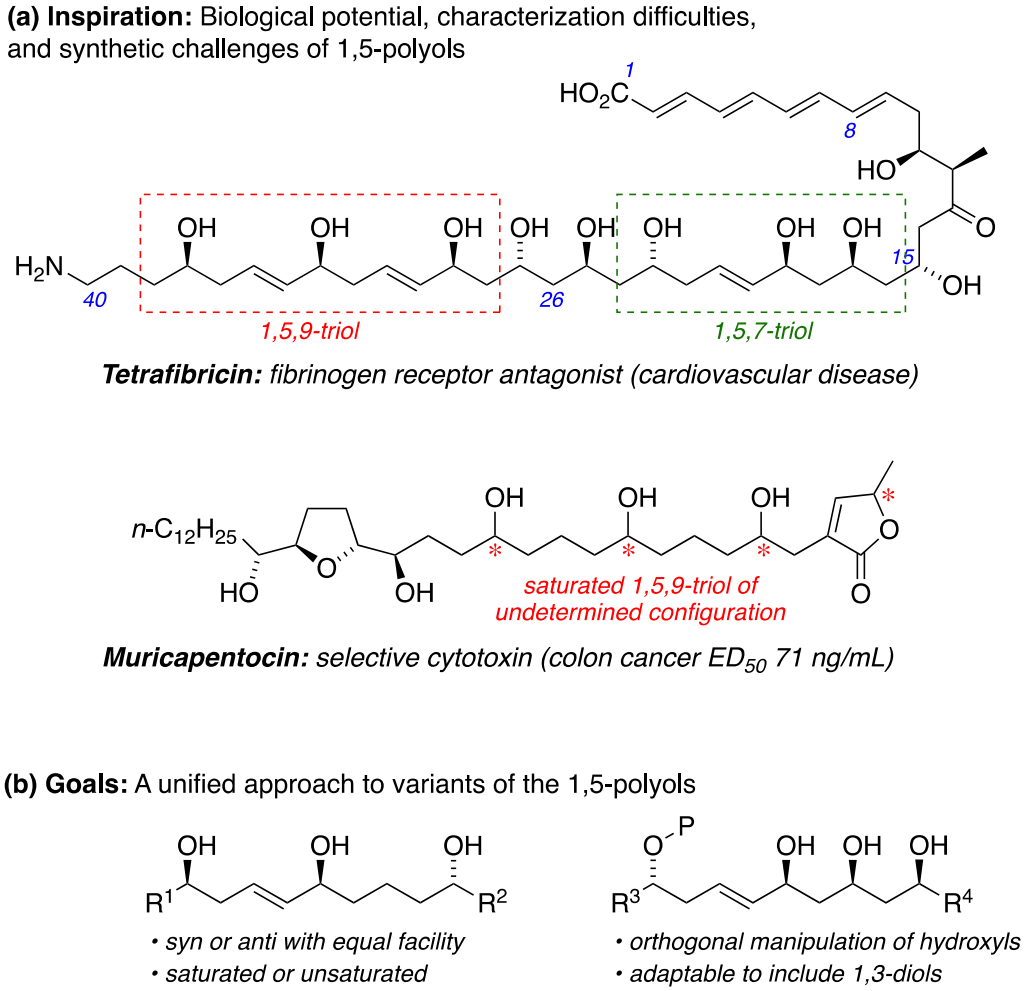


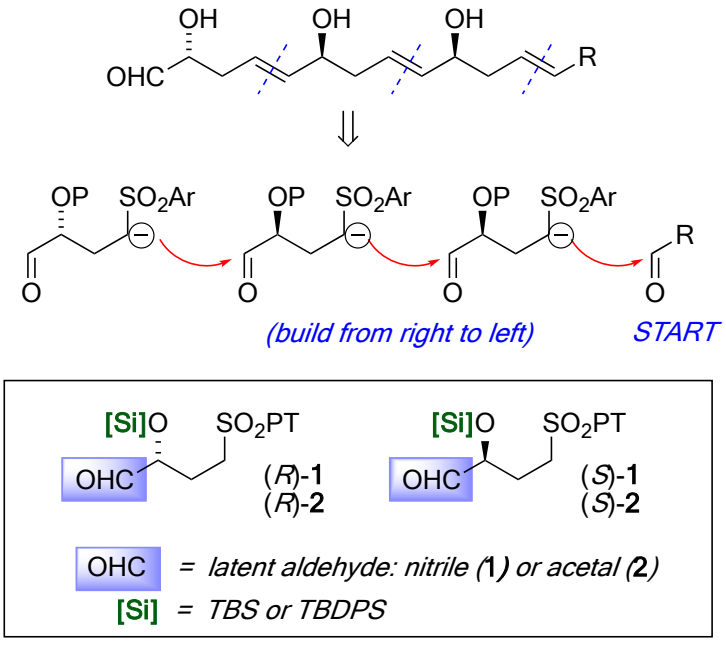
Figure 1. Occurrence and importance of 1,5-polyol structures. (a) Bioactive natural products presenting the 1,5-polyol motif. (b) Targeted substructures for new strategic innovation.

To evade the aforementioned disadvantages, we envisioned an iterative strategy to access 1,5-polyols with unambiguous stereocontrol by encoding the configuration of each alcohol stereogenic center within repeating enantiopure building blocks prepared via asymmetric catalysis. Then, sequential coupling of these building blocks, choosing the correct configuration at each stage, would allow for preparation of any diastereomeric 1,5-polyol with equal facility, using the same coupling chemistry. For the coupling reactions, we chose the reliable Julia–Kocienski method,[20,21] using reagents readily available to most practitioners. Each building block would need sulfone and aldehyde termini, as depicted in α-siloxy-γ-sulfonyl aldehyde building block **1** (Scheme 1), with the aldehyde in latent form. In an iterative sequence, the

coupling would take place between the sulfone of **1** and the aldehyde of a growing 1,5-polyol chain; the latent aldehyde carried by the building block would then be revealed for another iteration of the Julia–Kocienski olefination. This is a strategy-level innovation that allows for the efficient and rapid access to *syn* and *anti* stereoisomers of a 1,5-polyol family from readily accessible materials, without the need to determine the configuration of each alcohol stereocenter in the growing polyol chain.

The development of the aforementioned strategy is presented in this full account,[22] detailing the design and enantioselective synthesis of a γ-hydroxysulfone building block and its implementation in preparation of various 1,5-polyol structures; the accompanying paper[23] describes application of this approach to a natural product of this class, tetrafibricin.

Scheme 1



2. Results and Discussion

Acetal Configuration-Encoded Building Block. In our initial attempt to implement the design hypothesis outlined in Scheme 1, acetal functionality was envisioned as a latent form of the aldehyde in configuration-encoded polyol building block because of (a) its orthogonality to

the Julia–Kocienski coupling conditions, and (b) its expected ease of hydrolysis. To test this, we then needed access to α-silyloxyaldehyde acetal with a structure exemplified by **2a** (Figure 2).

Examples of classical methods to access enantiopure α-silyloxyaldehydes are often unwieldy and limited, as we found in the course of other projects.[24] These include a six step sequence from malic acid to generate aldehyde **4**[25] and an eleven step sequence from D-mannitol to generate aldehyde **5**[26] (Figure 2b). Although Jacobsen's kinetic resolution[27] and organocatalytic α-oxidation of aldehydes[28] have offered improved alternatives to access to terminal 1,2-difunctional compounds, the selective manipulation of functionality in 1,2-diols can still be laborious. Thus, we devised a more direct and efficient route to α-silyloxyaldehydes and their corresponding acetal derivatives (e.g., **2**) via an oxidative sequence employing ring-opening of enol ester epoxides induced by a silyl electrophile (**A** → **B** → **C**).[29] Combining this proposed sequence with known access to enol esters from alkynes would lead to a generally useful protocol to prepare α-silyloxyaldehydes from alkynes.

Figure 2

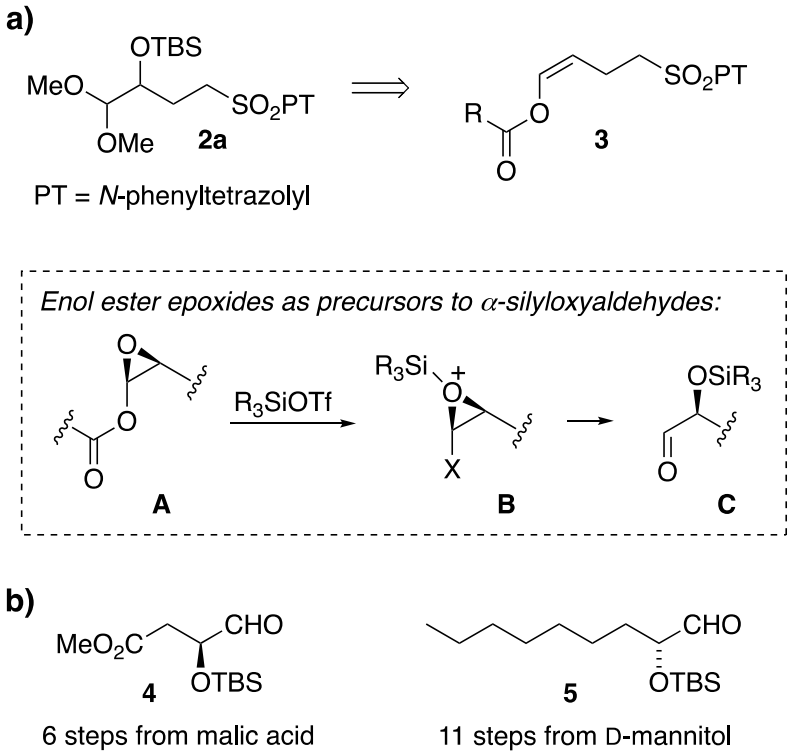
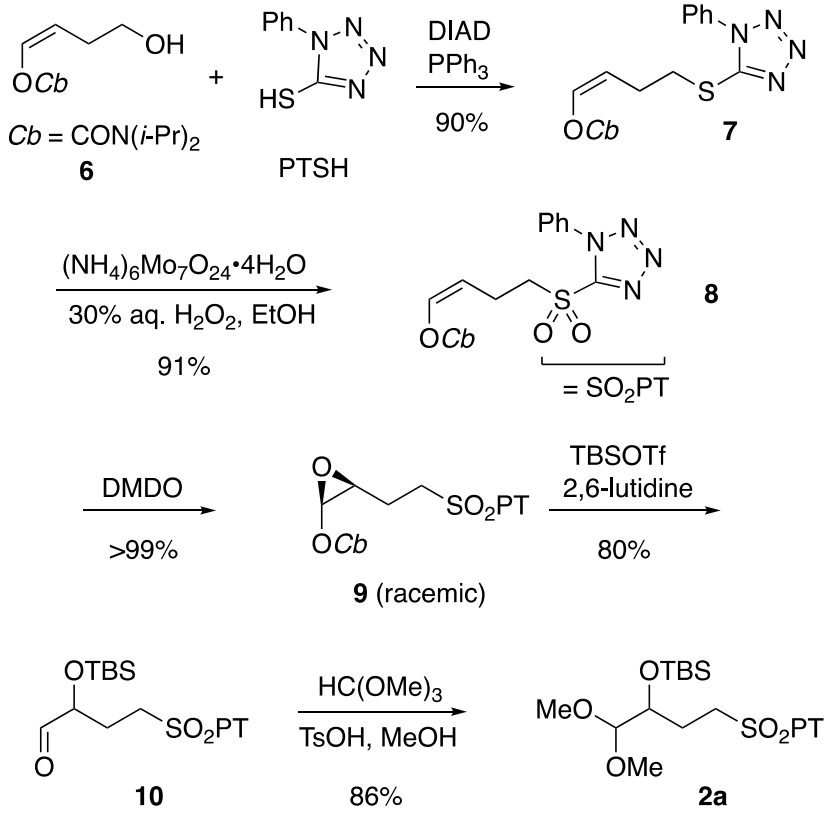


Figure 2. α-Silyloxyaldehyde synthesis. (a) Plan for silyl cation-induced ring-opening. (b) Selected examples of literature preparations.

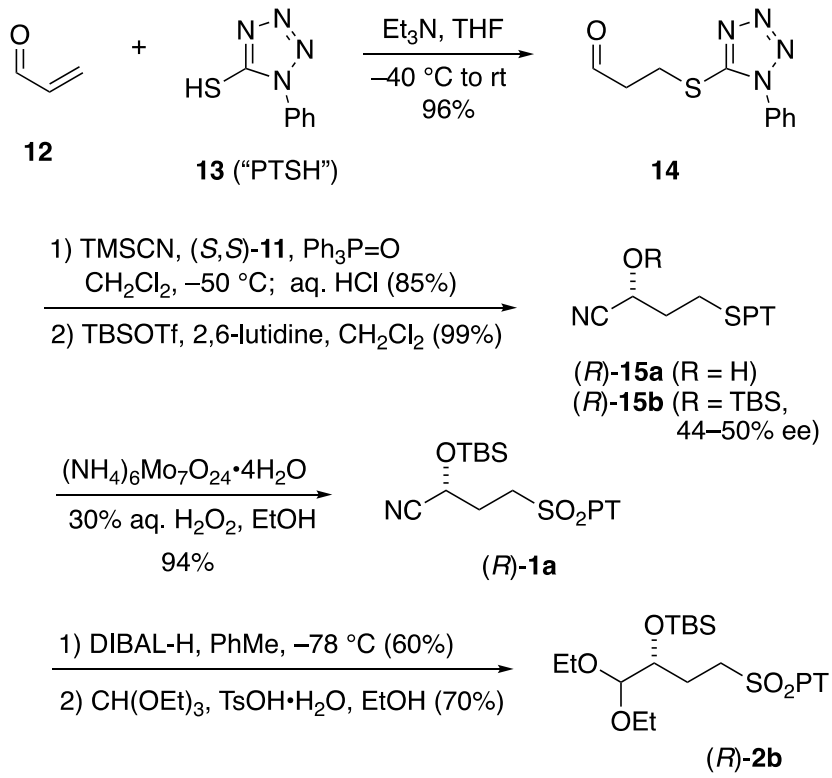
The required preparation of α-silyloxyaldehyde acetal **2a** presented an opportunity to test the feasibility of the hypothesized silyl cation-mediated epoxide-opening cascade. Thus, *Z*-enol ester **6** (Scheme 2) was generated using a homoenolate aldol reaction, homologating Hoppe's allyl carbamate anion[30] with formaldehyde in 74% yield. Mitsunobu reaction with *N*-phenyltetrazolylthiol followed by ammonium molybdate-catalyzed oxidation of sulfide **7** provided the corresponding sulfone **8**. The enol ester was next epoxidized with dimethyldioxirane (DMDO) to furnish chromatographically stable epoxide **9** in quantitative isolated yield. Upon treatment of **9** with TBSOTf and 2,6-lutidine at room temperature, aldehyde **10** was obtained in 80% yield, showing that the ring-opening pathway was indeed feasible. For characterization, the aldehyde was smoothly converted to the corresponding dimethyl acetal **2** in 86% yield under routine conditions ($HC(OMe)_3$, TsOH, MeOH). Subsequently, a brief scope study reported elsewhere[31] revealed that linking this enol ester epoxide opening cascade with the Goossen synthesis of enol esters from alkynes[32] produced a rapid three-step sequence to prepare α-silyloxyaldehydes from alkynes.

Scheme 2



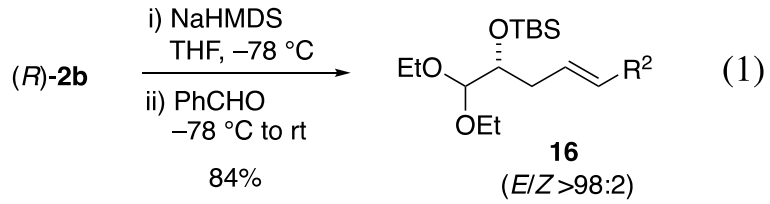
Although enantiomerically enriched α-silyloxyaldehyde **10** could potentially be accessed by employing an asymmetric epoxidation[33] of ene-carbamate **8** prior to the epoxide opening, we also explored an alternative access via catalytic asymmetric cyanohydrin construction.[34] Most methods for this are not well-adapted to aliphatic aldehyde precursors,[35] but commercially available chiral C2-symmeric Al(salen) catalyst **11** showed promise in such cases.[36] This approach began by engaging acrolein (**12**) in a conjugate addition reaction with 1-phenyltetrazolyl-5-thiol (PTSH, **13**) in the presence of catalytic triethylamine; this provided the 3-thiopropanal derivative **14** in 95% yield on multi-gram scale. Asymmetric addition of TMSCN in the presence of Al(salen) catalyst (*S*,*S*)-**11** (1 mol%) and additive Ph_3PO (10 mol%) at low temperature furnished an *O*-TMS cyanohydrin that proved difficult to handle and store. However, following the cyanation with an aqueous acidic workup afforded the free cyanohydrin **15a** in 85% yield. A more robust silyl protecting group (TBS) was then installed under standard conditions to provide *O*-silyl cyanohydrin (*R*)-**15b** in 84% yield; at this stage chiral HPLC indicated ee values in the range of 44–50% for this sequence.[37] Oxidation with peroxide under ammonium molybdate catalysis gave the corresponding sulfone (*R*)-**1a**. Then, reduction of the nitrile (DIBAL-H) and treatment of the resulting α-silyloxyaldehyde with triethyl orthoformate and catalytic TsOH furnished acetal (*R*)-**2b** in moderate yield.

Scheme 3



With two acetal versions of the configuration-encoded building block in hand (**2a** and (*R*)-**2b**), Julia–Kocienski couplings were next examined. Several preliminary experiments with **2a** indicated that sequential treatment with base and benzaldehyde, isobutyraldehyde, or (*S*)-2-*tert*-butyldimethylsiloxypropanal led to successful olefination.[38] In order to render this an iterative process, acetal hydrolysis would next be needed, and unfortunately numerous efforts to achieve this resulted in complex mixtures. Precedent suggested that the diethyl acetal might be more easily hydrolyzed.[39]

Equation 1

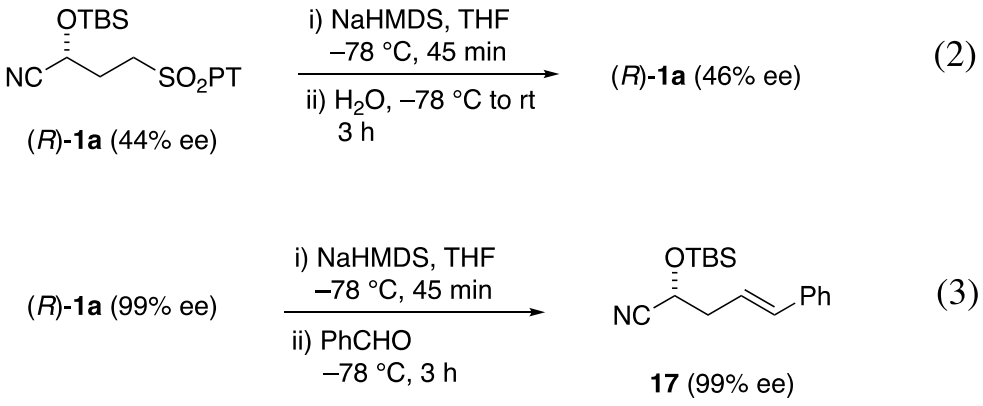


(1)

Toward this objective, Julia–Kocienski coupling of (*R*)-**2b** with benzaldehyde (Equation 1) furnished alkene **16** (*E*/*Z* > 98:2). Considerable effort was dedicated to screening various conditions for acetal hydrolysis of **16**. Under all conditions attempted, the material was either returned unchanged or produced intractible mixtures and low mass balance.[40] Eventually, we concluded that the silyl protection was not sufficiently orthogonal to acetal hydrolysis in this instance. Nevertheless, the promising Julia–Kocienski couplings were encouraging toward further exploration of the configuration-encoded strategy for 1,5-polyol synthesis.

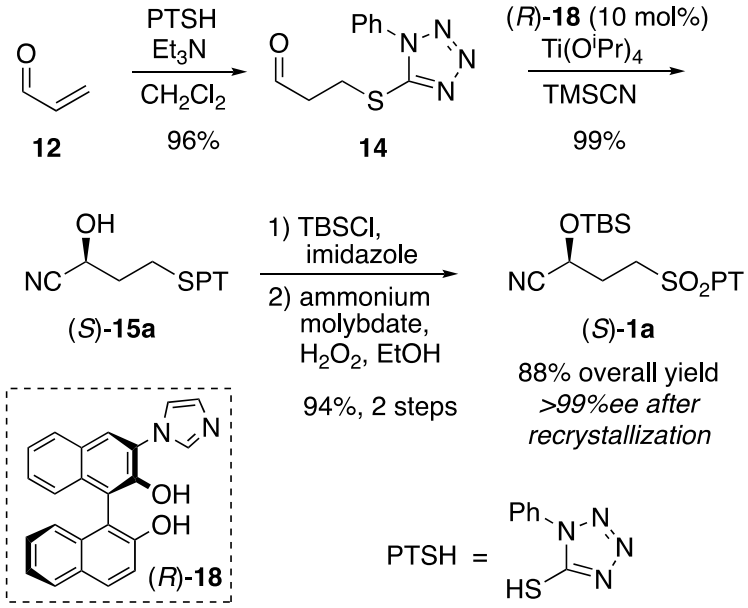
Nitrile Configuration-Encoded Building Block. Cyanohydrin (*R*)-**1a**, obtained along the synthetic route to acetal **2b** (Scheme 3), was not initially prioritized due to concerns about racemization under Julia–Kocienski coupling conditions.[41] However, the orthogonality problem observed during attempted hydrolysis of **16** refocused our attention on (*R*)-**1a** because it would allow unmasking of the latent α-silyloxyaldehyde by hydride reduction instead of hydrolysis. Fortunately the racemization concerns were eliminated by two key experiments that established retention of the *O*-silylcyanohydrin configuration during sulfone metalation. First, deprotonation of (*R*)-**1a** (44% ee) with NaHMDS and quenching with water (Equation 2) returned (*R*)-**1a** (99% recovery) with complete retention of the enantiomeric excess, as judged by HPLC. Secondly, enantiopure (*R*)-**1a** (prepared by a different method, *vide infra*) was exposed to the same metalation conditions followed by Julia–Kocienski coupling with benzaldehyde (Equation 3), and HPLC analysis of the isolated product **17** again indicated complete retention (99% ee).

Equations 2 and 3



Improved enantioselectivity in the cyanation step was eventually achieved using a chiral Ti catalyst generated from a bifunctional BINOL ligand introduced for cyanation by Gau and You.[42] Thus, reaction of aldehyde **14** with excess TMSCN and the catalyst generated in situ from Ti(O*i*Pr)$_4$ and chiral ligand (*R*)-**18** at –20 °C afforded cyanohydrin (*S*)-**15a** (Scheme 4). At 1 mol% catalyst loading, the reaction proceeded in 67% yield and 33% ee (HPLC after conversion to the *O*-TBS derivative (*S*)-**15b**). Screening catalyst loadings of 5, 8, and 10 mol% revealed that the yields reached 85–90% at 5 mol%, but the selectivity was only 78% ee, even at 10 mol%. Lowering the temperature to –50 °C improved both yield and selectivity, affording a 99% yield and 90% ee.[43]

Scheme 4



The optimized sequence (Scheme 4) furnished similarly high yields and selectivities for both enantiomeric sulfone building blocks (*R*)- and (*S*)-**1a**, and was easily scalable to approximately 10 grams. The chiral ligand **18** was isolated with a recovery of 70–90%, and was successfully re-used in the sequence. Absolute configuration in the series leading to (*R*)-**1a** was assigned using MPA ester analysis; desilylation of (*R*)-**1a** (TsOH in aq. MeOH) and separate EDCI-mediated esterifications with (*R*)- and (*S*)-methoxyphenyl acetic acid smoothly furnished the MPA esters for this purpose.[44]

Although material of 90% ee may be suitable for many synthetic applications, we recognized that the proportion of desired stereoisomer would diminish at each stage if this level of purity were to be employed in an iterative sequence. In considering how to bolster enantiopurity, we noted that a solid was formed after the final oxidation step to sulfone **1a** (Scheme 4), so recrystallization from ethyl acetate/petroleum ether was examined. Fortuitous observations during early attempts revealed that careful physical separation of crystals of two different habits (Figure 3) offered enantiomeric resolution.[45] Crystals appearing as transparent prisms of approximately 1-4 mm proved to be racemic, and those appearing as a white powder (very fine colorless needles on closer inspection) were enantiomerically pure, as judged by HPLC. Subsequently, we noticed that the racemic material could be selectively crystallized in the first crystallization, and then the second and third crops furnished **1a** with the ee enriched to >99% (HPLC).

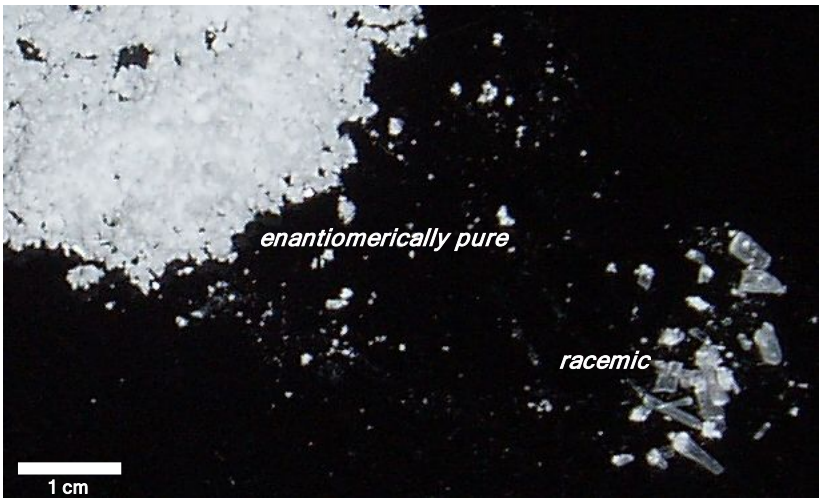
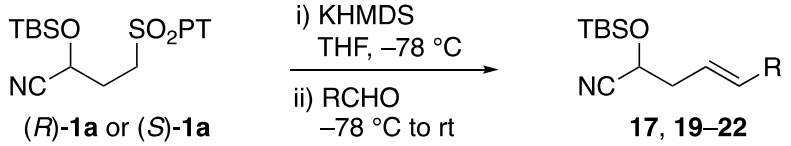


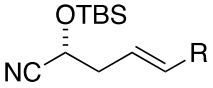
Figure 3. Two different crystal habits obtained upon recrystallization of enantiomerically enriched **1a** from EtOAc and petroleum ether. At top left, very fine colorless needles of enantiomerically pure **1a**. At bottom right, larger prisms of racemic **1a**.

Application to Iterative 1,5-Polyol Synthesis. Preliminary studies of the application of nitrile configuration-encoded building block **1a** confirmed the utility of both enantiomers in Julia–Kocienski couplings with simple unfunctionalized aldehydes, affording alkenes **17** and **19** (Table 1).[22] Screening of Julia–Kocienski conditions revealed very high yields and *E*-selectivities were obtained using either NaHMDS or KHMDS in THF at low temperature. Coupling reactions employing the sodium and potassium counterions were roughly similar in their *E*-selectivity, but LiHMDS led to noticeably lower selectivity. Coupling of **1a** with α-silyloxyaldehydes derived from lactic acid or leucine showed the feasibility of constructing diastereomeric 1,5-diols exemplified by **20** and **21**.

Table 1. Julia–Kocienski Couplings of **1a**.

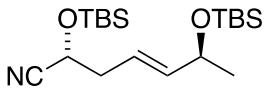


Using (*R*)-**1**:

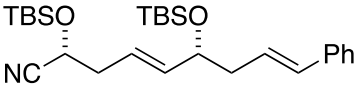


17 (R = Ph), 99% (*E*/*Z* >98:2)

19 (R = *i*-Pr), 96%[b] (*E*/*Z* 95:5)

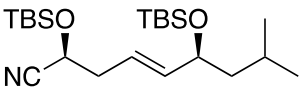


20, 95% (*E*/*Z* >98:2)

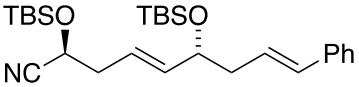


(*R*,*R*)-**22**, 99% (*E*/*Z* >95:5)

Using (*S*)-**1**:



21, 99% (*E*/*Z* >95:5)

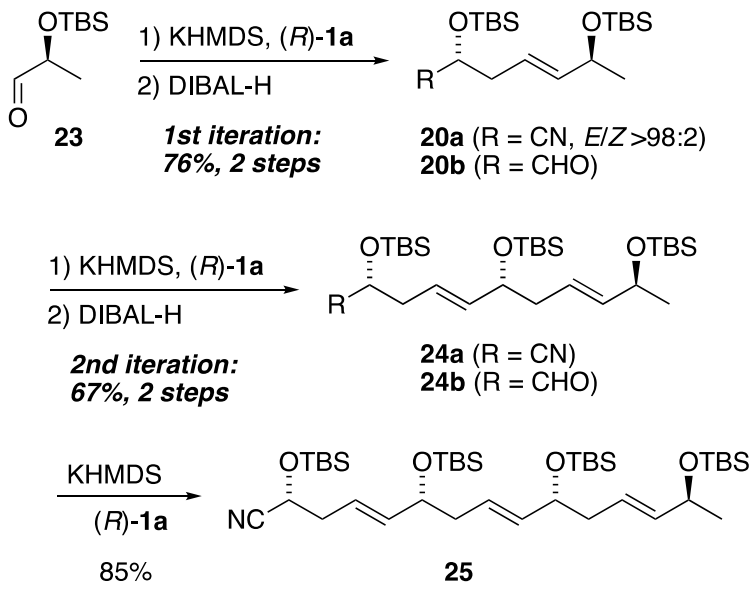


(*S*,*R*)-**22**, 99% (*E*/*Z* >95:5)

[a] Conditions: **1a**, KHMDS (1.2 equiv), THF, –78 °C, 45 min; then RCHO (1.0 equiv), –78 °C to ambient temperature. *E*/*Z* ratios measured by integration of ^{1}H NMR spectra. [b] NaHMDS was employed.

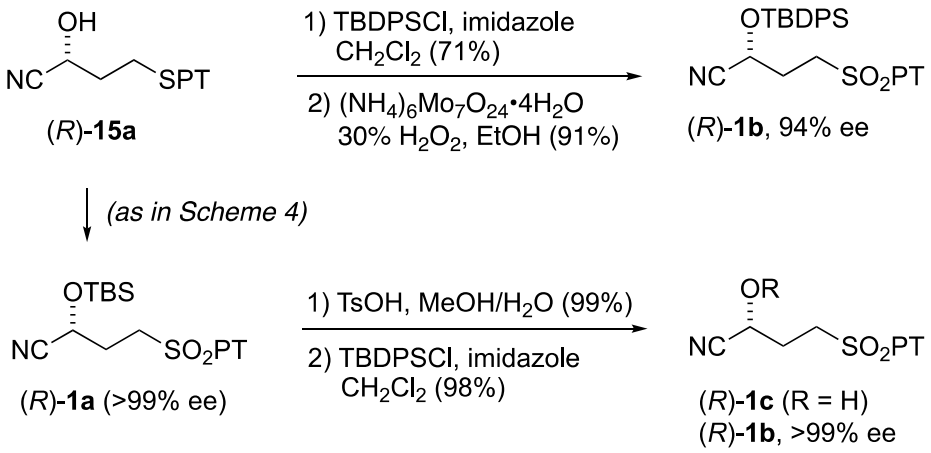
Next, iterative application of the configuration-encoded synthesis required exposing the reactive aldehyde at the polyol terminus. Reaction of nitrile **17** to DIBAL-H led to the corresponding aldehyde, used in turn as the precursor for separate coupling experiments with *R* and *S* configurations of the γ-sulfononitrile building block **1a** to afford diastereomerically pure samples of (*R*,*R*)-**22** and (*S*,*R*)-**22**. These two successive Julia–Kocienski couplings were carried out with enantiomeric building blocks, furnishing both the *syn* and *anti* diastereomers of **22** under otherwise identical conditions, and highlighting the simplicity with which this strategy controls relative stereochemistry. The iterative nature of the approach was demonstrated to three successive couplings upon *O*-silyl-lactaldehyde **23**, affording convenient access to 1,5,9,13 tetraol **25** in diastereomerically pure form (Scheme 5).

Scheme 5



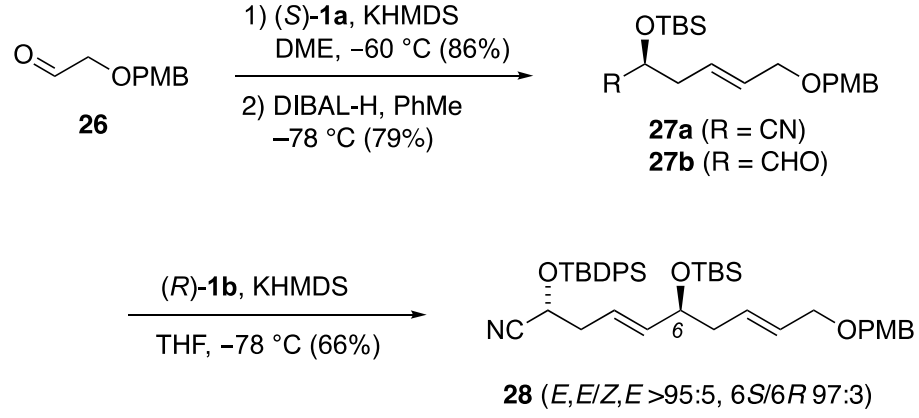
Hydroxyl Differentiation. Selective manipulations of the hydroxyl groups of a 1,5-polyol may be desired in certain synthetic contexts, such as ensuring the correct ring size in macrolactonization. To address this, we sought to replace the *tert*-butyldimethylsilyl group in building block (*R*)-**1a** with an alternative silyl group. We opted for the modulated reactivity approach, allowing for selective removal of TBS from a 1,5-polyol in the presence of a *tert*-butyldiphenylsilyl (TBDPS). The most direct route to this alternative building block (*R*)-**1b** (Scheme 6) follows the same sequence as for the TBS-protected analog, beginning with the asymmetric cyanation of aldehyde **14**. Silylation of cyanohydrin (*R*)-**15a** with TBDPSCl and imidazole, followed by oxidation with ammonium molybdate smoothly furnished (*R*)-**1b**. Unfortunately this waxy solid was not amenable to enantioenrichment via recrystallization.

Scheme 6



We returned to further optimize the cyanation step, and eventually, we found that allowing more time in between the slow addition of reagents and careful temperature control in cannula transfer, we were able to increase the enantioselectivity in the cyanation step to 94% ee without lower temperature and unacceptably long reaction time. Others have speculated that the condition of the TMSCN reagent may lead to variable selectivity due to the variations in the amount of HCN present.[41a] Although the cyanohydrin (*R*)-**15a** (75% yield) was smoothly transformed to the sulfone building block (*R*)-**1b** of 94% ee, enantiopure material (99% ee or higher) was desired. An alternate route achieved this. Removal of the TBS group from the TBS-protected (*R*)-**1a** (>99% ee after recrystallization) with *p*-TsOH afforded cyanohydrin (*R*)-**1c** (99% yield) with no erosion of enantiopurity (as judged by optical rotation after reinstallation of the TBS group). Installation of the TBDPS group as before furnished enantiopure alternate α-siloxy-γ-sulfononitrile building block (*R*)-**1b** in 98% yield (>99% ee as judged by HPLC).

Scheme 7



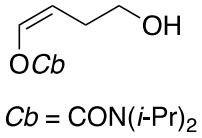
With both TBS and TBDPS building blocks of high enantiopurity at hand, their application in iterative coupling was examined (Scheme 7). Julia–Kocienski coupling of glycolaldehyde derivative **26**[46] with building block (*S*)-**1a** (KHMDS in 1,2-dimethoxyethane) gave olefin **27a** in 86% yield and *E*/*Z* = 90:10 (by ^{1}H NMR and confirmed by GC-HRMS). Hydride reduction (DIBAL-H, toluene) furnished aldehyde **27b** (79% yield). In this case the workup required some optimization to minimize racemization;[47] the optimized protocol entailed washing the crude with very dilute (0.1 mM) aqueous tartaric acid and promptly using the aldehyde in the next step. Another iteration of the Julia–Kocienski coupling, this time with alternative sulfone building block (*R*)-**1b** bearing a TBDPS-protected hydroxyl, furnished *anti*-1,5-diol **28** in 66% yield with excellent selectivity (*E*,*E*/*Z*,*E* >95:5, 19*S*/19*R* 97:3). This sequence demonstrates that the configuration-encoded 1,5-polyol synthesis can be accomplished with differential protection, opening the option of selective functionalization at one specific hydroxyl among many.

3. Conclusion

In conclusion, efficiency and selectivity advantages have been demonstrated in a configuration-encoded iterative approach to 1,5-polyol synthesis. Enantioselective and scalable preparation of γ-sulfonyl-α-silyloxylaldehyde building blocks, with the aldehyde functionality in latent form, enables convenient and reliable coupling chemistry with reagents that are readily available in most synthesis laboratories. Importantly, encoding the alcohol configurations within the building block mitigates the analytical and separations challenges inherent to alternative approaches that generate new stereogenic centers in the coupling events. Extension to a differentially protected 1,5,9-triol and a 1,5,9,13-tetraol indicate there is considerable potential for broader applications in synthesis of complex molecular targets in the 1,5-polyol class.

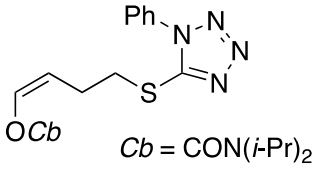
Experimental Section

Materials and Methods. Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. THF, diethyl ether, CH_2Cl_2, benzene and toluene were purchased inhibitor-free, sparged with argon, and passed through columns of activated alumina prior to use (dropwise addition of blue benzophenone ketyl solution revealed the THF purified in this manner sustained the blue color more readily than the control sample purified by distillation). Nitrogen was passed successively through columns of anhydrous $CaSO_4$ and R3-11 catalyst for removal of water and oxygen, respectively. All other materials were used as received from commercial sources unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with UV indicator. Flash chromatography columns were packed with 230-400 mesh silica gel as a slurry in the initial elution solvent. Gradient flash chromatography was conducted by adsorption of product mixtures on silica gel, packing over a short pad of clean silica gel as a slurry in hexane, and eluting with a continuous gradient from hexane to the indicated solvent. Radial chromatography refers to centrifugally accelerated thin-layer chromatography performed with a Chromatotron using commercially supplied rotors. Melting points are uncorrected. Nuclear magnetic resonance (NMR) data were obtained at operating frequencies of 600, 500, 400, or 300 MHz for ^{1}H and 150, 125, 100 or 75 MHz for ^{13}C, respectively. Infrared spectra were recorded using a single beam FT-IR spectrophotometer by standard transmission methods or by use of an attenuated total reflectance (ATR) probe. Optical rotations were determined using a digital polarimeter operating at ambient temperature. Low- and high-resolution mass spectra were obtained using sample introduction by dip, liquid chromatography or gas chromatography. Combustion analyses were obtained from external commercial services. Chromatographic diastereomer ratio analyses employed GCMS with 15 mL x 0.25 mm I.D. x 0.25 μ F.T. 5%-phenyl-95%-dimethylsiloxane column and helium as mobile phase or HPLC with Microsorb-MV Si 8um 100A or Chiralcel OD columns (2-propanol/hexane as mobile phase) or Chirex 3014 column (chloroform/hexane as mobile phase).



6

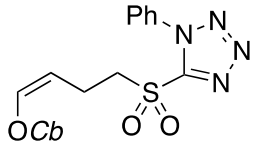
(*Z*)-4-Hydroxybut-1-enyl diisopropylcarbamate (6). To a solution of *O*-allyl *N*,*N*-diisopropylcarbamate (150 mg, 0.81 mmol) and (–)-sparteine (0.23 mL, 0.97 mmol) in toluene (7.5 mL) at –78 °C was added *n*-BuLi (0.43 mL, 0.97 mmol) slowly over a period of 30 min. After 2 h at –78 °C, a chilled (–78 °C) solution of fresh titanium tetraisopropoxide (0.67 mL, 2.4 mmol) in toluene (2 mL) was added dropwise. After 30 min at –78 °C, a solution of formaldehyde in THF (0.37 M, 5.06 mL, 1.62 mmol) was added. After 1 h at –78 °C, the reaction was allowed to warm to room temperature, quenched with saturated aq. NH_4Cl (5 mL), and partitioned between cold 2N aq. HCl (15 mL) and diethyl ether (30 mL). Concentration and gradient flash chromatography (petroleum ether to 40% EtOAc in petroleum ether) afforded *Z*-enol ester **6** (128 mg, 73.9% yield) as a colorless oil; (IR (film) 3440, 2974, 2934, 1712, 1687, 1442, 1307, 1062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (ddd, *J* = 6.4, 1.3, 1.3 Hz, 1H), 4.76 (dd, *J* = 13.8, 7.2 Hz, 1H), 4.07 (m, 1H), 3.83 (m, 1H), 3.67 (dd, *J* = 6.9, 6.6 Hz, 2H), 2.43 (m, 2H), 1.25 (d, *J* = 5.7 Hz, 12H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) 153.0, 137.4, 106.8, 62.3, 47.0, 45.9, 28.9, 21.7, 20.5; MS (ESI) *m*/*z* (relative intensity) 216 ($[M+H]^+$, 77%), 333 (27%), 282 (100%); HRMS (ESI-TOF) Calcd. for $C_{11}H_{21}NaNO_3$ ($[M+Na]^+$): 238.1419, Found: 238.1437.



7

(*Z*)-4-(1-Phenyl-1*H*-tetrazol-5-ylthio)but-1-enyl diisopropylcarbamate (7). To a solution of **6** (51 mg, 0.24 mmol), 1-phenyltetrazol-5-ylthiol (211.1 mg, 1.184 mmol) and triphenylphosphine (310.8 mg, 1.184 mmol) in THF (1 mL) at 0 °C was added dropwise a solution of diisopropyl azodicarboxylate (335.3 mg, 1.658 mmol) in THF (1 mL). After 2 h at room temperature, concentration and gradient flash chromatography (petroleum ether to 20% EtOAc in petroleum

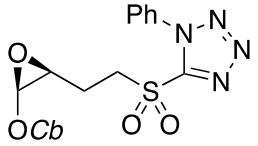
ether) afforded sulfide **7** (79 mg, 90% yield) as a colorless viscous oil; IR (film) 2967, 1707, 1497, 1433, 1299, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58-7.52 (m, 5H), 7.12 (ddd, *J* = 6.3, 1.2, 1.2 Hz, 1H), 4.81 (dd, *J* = 13.8, 7.2 Hz, 1H), 4.01 (m, 1H), 3.83 (m, 1H), 3.46 (dd, *J* = 7.2, 6.6 Hz, 2H), 2.74 (m, 2H), 1.21 (d, *J* = 6.3 Hz, 12H); $^{13}C\{1H\}$ NMR (75 MHz,$CDCl_3$) δ 154.3, 152.6, 137.4, 133.8, 130.3, 130.0, 123.9, 107.1, 46.9, 46.0, 33.1, 24.9, 21.5, 20.5; MS (ESI) *m/z* (relative intensity) 398 ($[M+Na]^+$, 22%), 333 (15%), 282 (100%); HRMS (ESI-TOF) Calcd. for $C_{18}H_{26}N_5O_2S$ ($[M+H]^+$): 376.1807, Found: 376.1812.



Cb = CON(*i*-Pr)$_2$

8

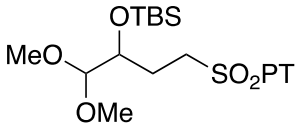
(*Z*)-4-(1-Phenyl-1*H*-tetrazol-5-ylsulfonyl)but-1-enyl diisopropylcarbamate (8). To a solution of sulfide **7** (27 mg, 0.072 mmol) in ethanol (0.8 mL) at 0 °C was added a cooled (0 °C) solution of ammonium molybdate tetrahydrate (17.8 mg, 0.0144 mmol) in 30% aqueous hydrogen peroxide (1.2 mL, 1.1 mmol). After 12 h at ambient temperature, the reaction mixture was partitioned between water (5 mL) and EtOAc (25 mL). Concentration and radial chromatography (20% EtOAc in petroleum ether) afforded sulfone **8** (26.3 mg, 90.7% yield) as a colorless solid. IR (film) 2973, 2926, 2250, 1707, 1468, 1427, 1345, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70-7.64 (m, 2H), 7.63-7.55 (m, 3H), 7.14 (ddd, *J* = 6.3, 1.5, 1.2 Hz, 1H), 4.75 (m, 1H), 3.96 (m, 2H), 3.79 (m, 2H), 1.24 (d, *J* = 6.9 Hz, 12H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 153.5, 152.1, 138.2, 133.1, 131.6, 129.9, 125.2, 104.2, 55.5, 46.9, 46.4, 21.6, 20.5, 18.6; MS (ESI) *m/z* (relative intensity) 408 ($[M]^+$, 20%), 430 ($[M+Na]^+$, 45%), 282 (100%); HRMS (ESI-TOF) Calcd. for $C_{18}H_{26}N_5O_4S$ ($[M+H]^+$): 408.1706, Found: 408.1717.



Cb = CON(*i*-Pr)$_2$

9 (racemic)

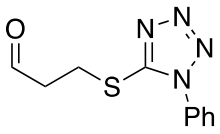
3-(2-(1-Phenyl-1*H*-tetrazol-5-ylsulfonyl)ethyl)oxiran-2-yl diisopropylcarbamate (9). To a solution of enol ester **8** (26.3 mg, 0.0645 mmol) in acetone (1.5 mL) at –10 °C was added a solution of dimethyl dioxirane in acetone (10 mL, prepared from a mixture of acetone, water, sodium bicarbonate and Oxone). After 5 h at ambient temperature, concentration and radial chromatography (35% EtOAc in petroleum ether) afforded epoxide **9** (27.3 mg, quantitative yield) as a colorless oil; IR (film) 2973, 2936, 1710, 1693, 1499, 1433, 1349, 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72-7.66 (m, 2H), 7.63-7.56 (m, 3H), 5.63 (d, *J* = 2.4 Hz, 1H), 3.97-3.80 (m, 4H), 3.20, (m, apparent dt, *J* = 6.0, 6.0, 2.1 Hz, 1H), 2.49-2.36 (m, 2H), 1.24 (d, 6H), 1.20 (d, 6H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 153.5, 153.4, 133.1, 131.8, 130.0, 125.2, 76.2, 53.7, 53.2, 46.9, 46.5, 21.5; MS (ESI) *m*/*z* (relative intensity) 446 ($[M+Na]^+$, 100%), 279 (36%), 216 (35%); HRMS (ESI-TOF) Calcd. for $C_{18}H_{26}N_5O_5S$ ($[M+H]^+$): 424.1655, Found: 424.1662.



2a (racemic)

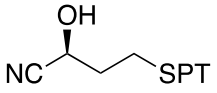
5-(3-(*tert*-Butyldimethylsilyloxy)-4,4-dimethoxybutylsulfonyl)-1-phenyl-1*H*-tetrazole (2a). To a solution of epoxide **9** (26 mg, 0.061 mmol) in CH_2Cl_2 (2 mL) were added 2,6-lutidine (0.028 mL, 0.12 mmol) and *tert*-butyldimethylsilyl triflate (0.034 mL, 0.074 mmol) at –10 °C. After 12 h at ambient temperature, the reaction mixture was partitioned between saturated aq. NH_4Cl and CH_2Cl_2 (20 mL). Concentration and flash chromatography (petroleum ether/EtOAc) afforded aldehyde **10** (20 mg, 80% yield) as a colorless oil that was immediately used in the next step. To a solution of aldehyde **10** (20 mg, 0.049 mmol) in methanol (1.5 mL) were added excess trimethylorthoformate (0.75 mL) and *p*-toluenesulfonic acid (1.9 mg, 0.0097 mmol). After 30 min, the reaction was the reaction mixture was partitioned between saturated aq. NH_4Cl and diethyl ether (25 mL). Concentration and flash chromatography (10% EtOAc in petroleum ether to 40% EtOAc in petroleum ether) afforded dimethyl acetal **2a** (18 mg, 86% yield) as a colorless oil; IR (film) 2930, 2856, 1499, 1463, 1342, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70-7.64 (m, 2H),

7.62-7.55 (m, 3H), 4.11 (d, *J* = 4.8 Hz, 1H), 3.95-3.78 (m, 3H), 3.43 (s, 3H), 3.41 (s, 3H), 2.19-2.12 (m, 2H), 0.89 (s, 9H), 0.09 (s, 6H); ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 153.5, 133.2, 131.6, 129.9, 125.3, 107.5, 71.1, 56.5, 56.3, 52.6, 29.9, 26.0, 25.1, 23.2, 18.3, -4.3, -4.7; HRMS (ESI-TOF) Calcd. for $C_{19}H_{32}N_4O_5NaSSi$ ([M+Na]$^+$): 479.1760, Found: 479.1767.



14

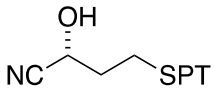
3-(1-Phenyl-1*H*-tetrazol-5-ylthio)propanal (14). To a solution of acrolein (0.52 mL, 7.9 mmol) in THF (8 mL) at –78 °C was added 1-phenyl-1*H*-tetrazole-5-thiol (1 g, 6 mmol) in THF (2 mL), followed by triethylamine (0.05 mL, 0.3 mmol). The mixture was stirred for 24 h at –5 °C. Concentration and gradient flash chromatography (petroleum ether to 30% EtOAc in petroleum ether) afforded **14** (1.26 g, 96.2% yield) as a colorless oil; IR (film) 3063, 2835, 2733, 1723, 1500, 1387 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.57-7.55 (m, 5H), 3.62 (t, *J* = 6.5 Hz, 2H), 3.18 (t, *J* = 6.5 Hz, 2H); ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 199.2, 153.9, 133.5, 130.2, 129.8, 123.7, 43.3, 25.2; MS (ESI) *m/z* (relative intensity) 235 ([M+H]$^+$, 100%), 257 ([M+Na]$^+$, 100%); HRMS (ESI-TOF) Calcd. for $C_{10}H_{11}N_4OS$ ([M+H]$^+$): 235.0654, Found: 235.0661.



(*S*)-**15a**

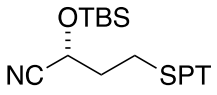
(*S*)-4-(1-Phenyl-1*H*-tetrazol-5-ylthio)-2-hydroxybutanenitrile ((*S*)-15a). Cyanation procedure using (*R*)-18 and Ti(O*i*-Pr)$_4$. A mixture of (*R*)-**18**[48] (1.29 g, 3.65 mmol) and Ti(O*i*-Pr)$_4$ (1.04 g, 3.65 mmol) in CH_2Cl_2 (50 mL) was stirred for 1 h at room temperature. TMSCN (9.8 mL, 73 mmol) was added at –50 °C and after 10 min, aldehyde **14** (8.6 g, 37 mmol) in CH_2Cl_2 (150 mL) was slowly added over 30 min. After 48 h at –50 °C, aq. HCl (2 N, 400 mL) and EtOAc (200 mL) were added at –50 °C [CAUTION: hydrogen cyanide may be evolved from acidified reaction mixtures and extraction fractions; these should be handled in a hood], and the mixture

was allowed to warm to room temperature. After 3 h, the mixture was extracted with EtOAc (600 mL). The organic phase was washed with brine and dried over Na_2SO_4. Concentration and flash chromatography (8% EtOAc in petroleum ether to 25% EtOAc in petroleum ether) afforded ligand **18** (92% recovery) and (*S*)-**15a** (9.5 g, 99% yield) as a pale yellow oil; IR (film) 3406, 2926, 2249, 1596, 1500, 1414, 1390, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62-7.54 (m, 5H), 4.89 (d, *J* = 6.6 Hz, 1H), 4.73 (ddd, *J* = 8.6, 6.6, 4.1 Hz, 1H), 3.61 (ddd, *J* = 14.6, 8.6, 5.7 Hz, 1H), 3.52 (ddd, *J* = 14.7, 5.9, 5.9 Hz, 1H), 2.49 (dddd, *J* = 14.4, 8.6, 5.7, 5.6 Hz, 1H), 2.36 (dddd, *J* = 14.7, 10.3, 6.2, 4.1 Hz, 1H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 154.9, 133.4, 130.8, 130.2, 124.1, 119.4, 58.8, 36.1, 28.6; MS (ESI) *m/z* (relative intensity) 262.04 ($[M+H]^+$, 30%), 235.04 (100%); Anal. Calcd. for $C_{11}H_{11}N_5OS$: C, 50.56; H, 4.24; N, 26.80. Found: C, 50.90; H, 4.43; N, 26.44. Enantiomer ratio and optical rotation measurements were made after *O*-silylation to avoid racemization. This run furnished material of 82.6%ee. In a separate run using lower temperature and longer reaction time (–60 °C, 93 h), from aldehyde **14** (0.4568 g, 1.748 mmol) was obtained cyanohydrin (*S*)-**15a** (0.4380 g, 85% yield); these conditions provided material of 97.7%ee.



(*R*)-**15a**

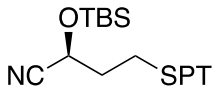
(*R*)-4-(1-Phenyl-1*H*-tetrazol-5-ylthio)-2-hydroxybutanenitrile ((*R*)-15a). Cyanation procedure using (*S*)-18 and Ti(O*i*-Pr)$_4$. Using the procedure as described for (*S*)-**15a**, from **14** (11.2 g, 47.9 mmol) and ligand (*S*)-**18**, was obtained (*R*)-**15a** (12.2 g, 97.6% yield); the recovery of ligand (*S*)-**18** was 71%. Enantiomer ratio and optical rotation measurements were made after the following step to avoid racemization.



(*R*)-**15b**

(*R*)-2-*tert*-Butyldimethylsilyloxy-4-(1-phenyl-1*H*-tetrazol-5-ylthio)butanenitrile (15b). Cyanation procedure using Al-Salen catalyst (*S*,*S*)-11. To a mixture of (*S*,*S*)-**11** (36.3 mg, 0.0598

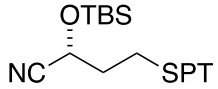
mmol) and triphenylphoshine oxide (166 mg, 0.598 mmol) in CH_2Cl_2 (23 mL) was added aldehyde **14** (1.2 g, 5.98 mmol) in CH_2Cl_2 (10 mL) at –50 °C. After 30 min, TMSCN (1.04 mL, 7.77 mmol) was added at –50 °C. After 20 h at –50 °C, aq. HCl (2 N, 100 mL) and EtOAc (200 mL) were added at –50 °C [CAUTION: hydrogen cyanide may be evolved from acidified reaction mixtures and extraction fractions; these should be handled in a hood], and the mixture was allowed to warm to room temperature. After 3 h, the mixture was extracted with EtOAc (600 mL). The organic phase was washed with brine and dried over Na_2SO_4. Concentration and flash chromatography (8% EtOAc in petroleum ether to 25% EtOAc in petroleum ether) afforded (*R*)-**15a** (1.1 g, 85% yield) as a pale yellow oil that was immediately subjected to the next step. To a solution of (*R*)-**15a** (115 mg, 0.44 mmol) in CH_2Cl_2 (3 mL) were added 2,6-lutidine (0.118 mL, 1.01 mmol) and TBSOTf (0.132 mL, 0.572 mmol) at room temperature. After 10 h, the reaction mixture was partitioned between water (200 mL) and CH_2Cl_2 (300 mL). The organic phase was washed with brine and dried over Na_2SO_4. Concentration and gradient flash chromatography (petroleum ether to 40% EtOAc in petroleum ether) afforded (*R*)-**15b** (139 mg, 84% yield, 50%ee) as a colorless oil.



(*S*)-**15b**

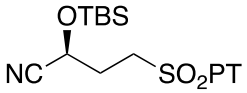
(*S*)-2-*tert*-Butyldimethylsilyloxy-4-(1-phenyl-1*H*-tetrazol-5-ylthio)-butanenitrile ((*S*)-15b). Multigram-scale procedure from cyanohydrin. To a solution of cyanohydrin (*S*)-**15a** (9.5 g, 36 mmol) in CH_2Cl_2 (550 mL) were added imidazole (6.6 g, 91 mmol) and *tert*-butyldimethylsilyl chloride (8.7 g, 55 mmol) at room temperature. After 18 h, the reaction mixture was partitioned between water (200 mL) and CH_2Cl_2 (300 mL). The organic phase was washed with brine and dried over Na_2SO_4. Concentration and gradient flash chromatography (petroleum ether to 40% EtOAc in petroleum ether) afforded (*S*)-**15b** (13.6 g, 98.9% yield, 82.6%ee) as a colorless oil; IR (film) 2955, 2931, 2886, 2858, 2238, 1500, 1413, 1389, 1255, 1113 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57-7.53 (m, 5H), 4.63 (dd, *J* = 6.2, 6.1 Hz, 1H), 3.59-3.43 (m, 2H), 2.44-2.37 (m, apparent q, 2H), 0.91 (s, 9H), 0.21 (s, 3H), 0.15 (s, 3H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 153.7, 133.7, 130.5, 130.1,

124.0, 119.3, 60.5, 35.7, 28.3, 25.7, 18.2, –5.0, –5.2; MS (ESI) *m/z* (relative intensity) 376.10 ([M+H]$^+$, 100%), 398.10 ([M+Na]$^+$, 20%); HRMS (ESI-TOF) Calcd. for $C_{17}H_{26}N_5OSSi$ ([M+H]$^+$): 376.1627, Found: 376.1628. HPLC retention times (Chiralcel OD-H, gradient elution from 0% to 40% *i*-PrOH in hexane over 40 min, 1mL/min): t_r 21.1 min (minor), t_r 22.1 min (major). A sample of 47%ee, obtained in a different run, gave $[\alpha]_D^{24}$ –17.8 (c 0.455, $CHCl_3$).



(*R*)-**15b**

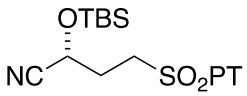
(*R*)-2-*tert*-Butyldimethylsilyloxy-4-(1-phenyl-1*H*-tetrazol-5-ylthio)-butanenitrile ((*R*)-15b). Multigram-scale procedure from cyanohydrin. Using the procedure described for (*S*)-**15b**, from (*R*)-**15a** (1.78 g, 6.81 mmol) was obtained (*R*)-**15b** (2.54 g, 99.6% yield, 86.0%ee). In a different run, a sample of 47.3%ee gave $[\alpha]_D^{23}$ +20.4 (c 0.435, $CHCl_3$).



(*S*)-**1a**

(*S*)-2-*tert*-Butyldimethylsilyloxy-4-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)butanenitrile ((*S*)-1a). To a solution of (*S*)-**15b** (302 mg, 0.804 mmol) in ethanol (9 mL) at 0 °C was added a solution of ammonium molybdate (20 mg, 0.016 mmol) in 30% aq. H_2O_2 (191 mg, 5.6 mmol). The reaction mixture was allowed to warm to room temperature. After 24 h, the reaction mixture was diluted with ethyl acetate (5 mL) and H_2O (5 mL), concentrated to remove ethanol, and partitioned between ethyl acetate and water. The organic phase was washed with brine and dried over Na_2SO_4. Concentration and gradient flash chromatography (petroleum ether to 40% EtOAc in petroleum ether) afforded (*S*)-**1a** (311 mg, 95.1% yield) as a colorless solid. Another run on 12 g scale afforded (*S*)-**1a** (11.6 g, 89.2% yield, 83.4%ee) as a colorless solid. Recrystallization from petroleum ether containing a small amount of ethyl acetate afforded analytically pure sample of (*S*)-**1a** (6.95 g, >99%ee) as a colorless fluffy mass of very fine needles; mp 69.5–70.5 °C; $[\alpha]_D^{26}$ –24.7 (c 0.530, $CHCl_3$); IR (film) 2955, 2932, 2859, 2492, 2361, 1498, 1464, 1344, 1150, 1114 cm^{-1}; ^{1}H

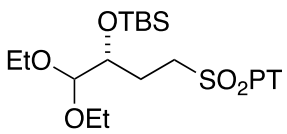
NMR (300 MHz, $CDCl_3$) δ 7.71-7.58 (m, 5H), 4.74 (dd, *J* = 5.8, 5.6 Hz, 1H), 4.03-3.86 (m, 2H), 2.56-2.48 (m, 2H), 0.93 (s, 9H), 0.23 (s, 3H), 0.18 (s, 3H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 131.9, 130.1, 125.2, 118.6, 59.8, 51.6, 29.7, 25.7, 18.3, –5.0, –5.1; MS (ESI) *m/z* (relative intensity) 407.9 (M^+, 55%), 408.9 ($[M+H]^+$, 25%), 215.87 (100%); Anal. Calcd. for $C_{17}H_{25}N_5O_3SSi$: C, 50.10; H, 6.18; N, 17.18. Found: C, 49.96; H, 6.20; N, 17.27. HPLC retention times (Chiralcel OD-H, gradient elution from 0% to 40% *i*-PrOH in hexane over 40 min, 1 mL/min): t_r 27.5 min (minor), t_r 29.1 min (major).



(*R*)-**1a**

(*R*)-2-*tert*-Butyldimethylsilyloxy-4-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)butanenitrile ((*R*)-1a). Using the procedure described for (*S*)-**1a**, from (*R*)-**15b** (10.8 g, 28.8 mmol) was obtained (*R*)-**1a** (10.9 g, 93.2% yield, 86%ee) as a colorless solid. Recrystallization from petroleum ether containing a small amount of ethyl acetate afforded analytically pure sample of (*R*)-**1a** (6.56 g, >99%ee) as colorless colorless fluffy mass of very fine needles; mp 69.5–70.0 °C; $[\alpha]_D^{25}$ +26.6 (c 0.935, $CHCl_3$).

Configurational Assignment of (*R*)-1a. Configuration of (*R*)-**1a** was assigned via NMR using MPA ester analysis according to the Riguera method.[49] After removal of the TBS group (TsOH, MeOH, H_2O, 99%), the resulting cyanohydrin (*R*)-**1c** was divided into two portions. Separate esterifications with (*S*)- and (*R*)-methoxyphenylacetic acid in the presence of EDCI and DMAP led to (*R*,*S*) MPA cyanohydrin ester (70% yield) and (*R*,*R*) MPA cyanohydrin ester (72% yield). The pair of diastereomeric MPA cyanohydrin esters were analyzed by proton and carbon NMR to determine the Δδ(R–S) values. With nitrile carbon numbering (CN = C1), the protons at C3 and C4 exhibited Δδ(R–S) of +0.11 and +0.35, respectively. For the CN carbon, Δδ(R–S) was –0.25. These data led to conclusive assignment of the (*R*)-configuration.

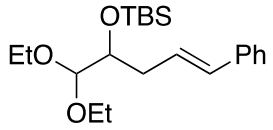


2b

5-(3-*tert*-Butyldimethylsilyloxy-4,4-(diethoxybutylsulfonyl)-1-phenyl-1H-tetrazole (2b). To a solution of racemic nitrile **1a** (552 mg, 1.35 mmol) in toluene (22 mL) at –78 °C was added DIBALH (1M in toluene, 1.63 mL, 1.63 mmol). After 1 h, the temperature was slowly raised to –20 °C over a period of 3 h. The reaction mixture was quenched with ethyl acetate (20 mL) at –20 °C, and then saturated aqueous sodium potassium tartrate (35 mL) was added. After 24 h, the mixture was filtered through a Celite pad and the filtrate was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4. Concentration and radial chromatography (40% EtOAc in petroleum ether) afforded unreacted nitrile **1a** (148 mg, 27% recovery) and aldehyde **10** (371 mg, 67% yield) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (d, *J* = 0.6 Hz, 1H), 7.68-7.62 (m, 5H), 4.24 (dd, *J* = 5.6, 0.6 Hz, 1H), 3.86-3.77 (m, 2H), 2.38- 2.30 (m, 2H), 0.94 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H). To a solution of aldehyde **10** (49 mg, 0.12 mmol) and triethylorthoformate (0.8 mL) in ethanol (4 mL) at room temperature was added toluenesulfonic acid (5 mg, 0.02 mmol). After 3 h, the reaction mixture was partitioned between sodium carbonate solution (10 mL) and ethyl acetate, and the organic phase was dried over Na_2SO_4. Concentration and radial chromatography (10% EtOAc in petroleum ether) afforded acetal **2b** (41 mg, 70% yield) as a colorless oil. The characterization sample was obtained from another run using enantiomerically pure (*R*)-**1a**. $[\alpha]^{21}_D$ = –1.65 (*c* = 1.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.66 (m, 2H), 7.63-7.56 (m, 3H), 4.28 (d, *J* = 4.8 Hz, 1H), 3.96-3.81 (m, 3H), 3.76-3.47 (m, 4H), 2.27-2.12 (m, 2H), 1.21 (t, *J* = 7.0 Hz, 6H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 154.4, 133.1, 131.4, 129.7, 125.1, 104.8, 71.4, 64.5, 64.2, 52.5, 25.8, 24.9, 18.1, 15.4, 15.2, -4.5, -4.9 ppm; HRMS (ESI-TOF) Calcd for $C_{21}H_{36}N_4O_5NaSiS$ ($[M+Na]^+$): 507.2073, Found 507.2076.

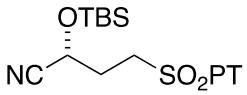
General Procedure A: Julia–Kocienski Reactions. To a solution of the sulfone (1 equiv) in THF (0.03 M) was added NaHMDS or KHMDS (1 M in THF, 1.2 equiv) at –78 °C. After 45 min, the requisite aldehyde (1 equiv) in THF (0.2 M) was added to the reaction mixture at –78 °C. After 3 h at –78 °C, the reaction mixture was quenched with aqueous NH_4Cl solution and allowed to warm to room temperature, then extracted with EtOAc. The organic phase was

washed with water and brine, then dried over Na_2SO_4. Concentration and radial chromatography (2%–7% EtOAc in petroleum ether) afforded the alkene products.



16

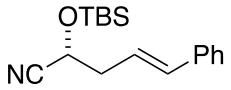
(*E*)-*tert*-Butyl-(1,1-diethoxy-5-phenylpent-4-en-2-yloxy)dimethylsilane (16). From **2b** (123 mg, 0.254 mmol) and benzaldehyde (53.9 mg, 0.508 mmol) via General Procedure A was obtained **16** (78 mg, 84% yield, *E*/*Z* >98:2) as a colorless oil. The characterization sample was obtained from another run using enantiomerically pure (*R*)-**2b**. $[\alpha]^{23}_D$ = -1.5 (*c* = 0.62, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.16 (m, 5H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.33-6.25 (m, 1H), 4.28 (d, *J* = 5.7 Hz, 1H), 3.78-3.65 (m, 3H), 3.64-3.53 (m, 2H), 2.56-2.38 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.90 (m, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 137.8, 131.9, 128.4, 127.3, 126.8, 126.8, 125.9, 105.2, 73.7, 64.0, 63.7, 36.6, 25.9, 18.2, 15.4, 15.3, -4.4, -4.6 ppm; HRMS (ESI-TOF) Calcd for $C_{21}H_{36}O_3SiNa$ ([M+Na]$^+$): 387.2331, Found 387.2330. A fraction enriched in the minor (*Z*)-isomer was obtained after careful radial chromatography, and its ^{1}H NMR spectrum showed an olefin peak at δ 6.50 (*J* = 11.8 Hz).



(*R*)-**1a**: Retention of Configuration

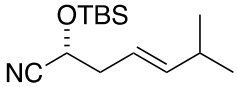
Retention of Configuration in Sulfononitrile (*R*)-1a under Julia–Kocienski reaction conditions. To a solution of sulfononitrile (*R*)-**1a** (40 mg, 0.098 mmol) of 44% ee (*R*/*S* 72:28 by HPLC) in THF (2 mL) was added NaHMDS (1 M in THF, 0.15 mL, 0.15 mmol) at –78 °C. After 3 h, the reaction mixture was quenched with water (2 mL) and allowed to warm to room temperature, then extracted with EtOAc. The organic phase was washed with water, brine, and then dried over Na_2SO_4. Concentration and radial chromatography (40% EtOAc in petroleum ether) afforded pure sulfononitrile (*R*)-**1a** (39 mg, 99% yield). Analysis by HPLC (Chiralcel OD-

H, gradient elution from 0% to 40% *i*-PrOH in hexane over 40 min, 1 mL/min) showed enantiomer ratio *R*/*S* of 73:27 (46% ee), indicating that no racemization was observed.



17a

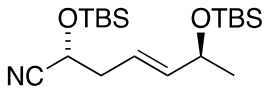
(*R*,*E*)-2-*tert*-Butyldimethylsilyloxy-5-phenylpent-4-enenitrile (17a). From (*R*)-**1a** (30 mg, 0.074 mmol) and benzaldehyde (7.8 mg, 0.074 mmol) via General Procedure A was obtained **17a** (24 mg, 99% yield, *E*/*Z* >98:2, 99%ee) as a colorless liquid; $[\alpha]_D^{24}$ +8.2 (c 1.1, $CHCl_3$); IR (film) 2955, 2931, 2886, 2858, 2312, 2230, 1471, 1362, 1255, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.22 (m, 5H), 6.56 (d, *J* = 15.9 Hz, 1H), 6.18 (ddd, *J* = 15.8, 7.3, 7.3 Hz, 1H), 4.50 (dd, *J* = 6.5, 6.5 Hz, 1H), 2.78-2.65 (m, 2H), 0.92 (s, 9H), 0.20 (s, 3H), 0.15 (s, 3H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 136.9, 135.3, 128.8, 128.0, 126.5, 122.4, 119.9, 62.4, 40.2, 25.8, 18.3, –4.9, –5.0; MS (EI) *m/z* (relative intensity) 287.2 (M^+, 1%), 230.1 ($[M–tBu]^+$, 80%), 117 (100%); Anal. Calcd. for $C_{17}H_{25}NOSi$: C, 71.03; H, 8.77; N, 4.87. Found: C, 71.08; H, 8.65; N, 4.81. HPLC retention times (Chiralcel AD-H, gradient elution from 0% to 40% *i*-PrOH in hexane over 40 min, 0.5 mL/min): t_r 14.0 min (major), t_r 16.1 min (minor).



19

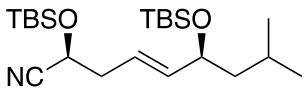
(*R*,*E*)-2-*tert*-Butyldimethylsilyloxy-6-methylhept-4-enenitrile (19). From (*R*)-**1a** (67.8 mg, 0.166 mmol) and 2-methylpropanal (12 mg, 0.17 mmol) via General Procedure A was obtained **19** (40.5 mg, 95.9% yield, *E*/*Z* 95:5) as a colorless liquid; $[\alpha]_D^{24}$ +18.3 (c 0.300, $CHCl_3$); IR (film) 2958, 2932, 2887, 2860, 2234, 1467, 1363, 1255, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (dddd, *J* = 15.4, 6.6, 1.1, 1.1 Hz, 1H), 5.34 (dddd, *J* = 15.4, 7.0, 7.0, 1.3 Hz, 1H), 4.36 (t, *J* = 6.6 Hz, 1H), 2.44 (m, apparent t, *J* = 6.9 Hz, 2H), 2.27 (m, 1H), 0.98 (d, *J* = 6.7 Hz, 6H), 0.90 (s, 9H), 0.17 (s, 3H), 0.12 (s, 3H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 143.6, 120.0, 119.5, 62.6, 39.8, 31.3, 25.7, 22.4, 18.3, –4.9, –4.1; MS (ESI) *m/z* (relative intensity) 276 ($[M+Na]^+$, 75%). HRMS (EI-TOF) Calcd. for

$C_{14}H_{27}NOSi$ (M^+): 253.1862, Found: 253.1867. For (*Z*)-**19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (dddd, *J* = 11.0, 9.3, 1.5, 1.5 Hz, 1H), 5.22 (dddd, *J* = 10.5, 7.2, 7.2, 1.2 Hz, 1H), 2.61-2.48 (m, 2H), other peaks were not resolved.



20a

(*E*,2*R*,6*S*)-2,6-Di(*tert*-butyldimethylsilyloxy)hept-4-enenitrile (20a). From (*R*)-**1a** (52 mg, 0.13 mmol) and (*S*)-2-*tert*-butyldimethylsilyloxypropanal[50] (24.3 mg, 0.128 mmol) via General Procedure A was obtained **20a** (86 mg, 95% yield, *E*/*Z* >98:2) as a colorless liquid; $[\alpha]_D^{25}$ +16.2 (c 0.815, $CHCl_3$); IR (film) 2957, 2930, 2887, 2858, 2308, 1472, 1255, 1114 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (dd, *J* = 15.5, 4.4 Hz, 1H), 5.59 (ddd, *J* = 15.4, 6.4, 5.9 Hz, 1H), 4.41 (dd, *J* = 6.3, 6.3 Hz, 1H), 4.30 (m, apparent br quintet, 6.3 Hz, 1H), 2.57-2.41 (m, 2H), 1.20 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H), 0.062 (s, 3H), 0.055 (s, 3H); ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 140.5, 120.9, 119.8, 68.8, 62.4, 39.4, 26.1, 25.7, 24.6, 18.5, 18.3, –4.4, –4.6, –4.9, –5.1; MS (ESI) *m/z* (relative intensity) 369.7 ($[M]^+$, 23%), 386.9 ($[M+NH_4]^+$, 45%); Anal. Calcd. for $C_{19}H_{39}NO_2Si_2$: C, 61.73; H, 10.63; N, 3.79. Found: C, 61.99; H, 10.90; N, 3.82. Under alternative experimental conditions (LiHMDS, toluene, –60 °C), the *E*/*Z* ratio was 71:29. For (*Z*)-**20a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (dddd, *J* = 11.1, 7.2, 7.2, 0.9 Hz, 1H), other peaks were not resolved.

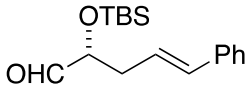


21

(*E*,2*S*,6*S*)-2,6-Di(*tert*-butyldimethylsilyloxy)-8-methylnon-4-enenitrile (21). From (*S*)-**1a** (150 mg, 0.368 mmol) and (*S*)-2-*tert*-butyldimethylsilyloxy-4-methylpentanal[49] (95 mg, 0.37 mmol) via General Procedure A was obtained **21** (150 mg, 98.6% yield, *E*/*Z* >95:5) as a colorless liquid; $[\alpha]_D^{25}$ –13.8 (c 0.835, $CHCl_3$); IR (film) 2956, 2930, 2859, 2238, 1471, 1362, 1256, 1113 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (dd, *J* = 15.5, 5.8 Hz, 1H), 5.55 (ddd, *J* = 15.4, 6.5, 6.5 Hz, 1H),

4.41 (dd, *J* = 6.3, 6.3 Hz, 1H), 4.13 (m, apparent q, *J* = 6.0 Hz, 1H), 2.51-2.46 (m, apparent t, *J* = 6.2 Hz, 2H), 1.77-1.59 (m, 1H), 1.42 (ddd, *J* = 13.7, 7.2, 7.2 Hz, 1H), 1.24 (ddd, *J* = 13.2, 7.2, 6.3 Hz, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.88 (d, *J* = 6.3 Hz, 6H), 0.18 (s, 3H), 0.13 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 139.9, 121.8, 119.8, 71.7, 62.3, 47.7, 39.4, 26.1, 25.7, 24.3, 23.2, 22.8, 18.4, 18.3, –3.9, –4.6, –4.9, –5.1; MS (ESI) *m/z* (relative intensity) 412.1 ([M+H]$^+$, 3%), 354.1 ([M–tBu]$^+$, 30%); HRMS (ESI-TOF) Calcd. for $C_{22}H_{45}NNaO_2Si_2$ ([M+Na]$^+$): 434.2887, Found: 434.2869.

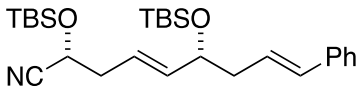
General Procedure B: DIBAL-H Reductions. The α-silyloxynitrile (1 equiv) was dissolved in toluene (0.04 M) and cooled to –78 °C. To this solution DIBAL-H (1 M in heptane, 1.5 equiv) was added at –78 °C. After 4 h, the reaction mixture was warmed slowly to –10 °C over period of 5 h, then quenched with methanol (2 mL) and warmed to room temperature. A saturated solution of sodium potassium tartrate (Rochelle's salt, 15 volumes) was added. After 12 h, the mixture was filtered over Celite, and the organic phase was washed with brine, dried over Na_2SO_4 and concentrated. Products were used directly without purification unless otherwise noted.



17b

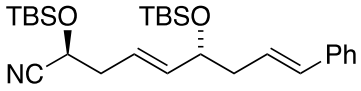
(*R*,*E*)-2-*tert*-Butyldimethylsilyloxy-5-phenylpent-4-enal (17b). From **17a** (64 mg, 0.22 mmol) via General Procedure B and radial chromatography (petroleum ether/EtOAc) was obtained **17b** (58.6 mg, 90.7% yield) as a colorless liquid; IR (film) 3028, 2954, 2930, 2857, 1737, 1471, 1463, 1255, 1115 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.2 Hz, 1H), 7.35-7.19 (m, 5H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.18 (ddd, *J* = 15.7, 7.3, 7.3 Hz, 1H), 4.09 (ddd, *J* = 7.0, 5.0, 1.5 Hz, 1H), 2.66-2.45 (m, 2H), 0.92 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 204.0, 137.3, 133.6, 128.7, 127.5, 126.3, 124.6, 95.8, 36.8, 25.9, 18.4, –4.5, –4.6; MS (EI) *m/z* (relative intensity) 290.2 (M$^+$, 0.5%), 233.1 ([M–*t*Bu]$^+$, 17%), 117.1 (100%). A sample of 95%ee, obtained in

a different run, gave $[\alpha]_D^{23}$ +1.9 (c 0.41, $CHCl_3$). This material was not sufficiently stable for combustion analysis.



(*R*,*R*)-22

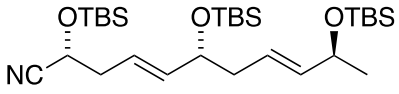
(2*R*,4*E*,6*R*,8*E*)-2,6-Di(*tert*-butyldimethylsilyloxy)-9-phenylnona-4,8-dienenitrile ((*R*,*R*)-22). From (*R*)-**1a** (117 mg, 0.287 mmol) and aldehyde **17b** (84 mg, 0.29 mmol) via General Procedure A was obtained (*R*,*R*)-**22** (119 mg, 88.2% yield, *E*/*Z* >95:5) as a colorless liquid; $[\alpha]_D^{23}$ +4.7 (c 0.675, $CHCl_3$); IR (film) 2955, 2930, 2887, 2858, 2238, 1472, 1463, 1256, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.17 (m, 5H), 6.41 (d, *J* = 15.9 Hz, 1H), 6.22 (ddd, *J* = 15.8, 7.2, 7.2 Hz, 1H), 5.72 (dd, *J* = 15.3, 5.4 Hz, 1H), 5.63 (ddd, *J* = 15.3, 7.2, 7.2 Hz, 1H), 4.41 (dd, *J* = 6.3, 6.3 Hz, 1H), 4.21 (m, apparent q, *J* = 6.3 Hz, 1H), 2.51 (m, apparent t, *J* = 6.5 Hz, 2H), 2.40 (m, apparent t, *J* = 7.0 Hz, 2H), 0.90 (s, 18H), 0.17 (s, 3H), 0.12 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 138.9, 137.8, 132.4, 128.7, 127.2, 126.8, 126.2, 122.2, 119.7, 73.0, 62.3, 42.3, 39.4, 26.0, 25.7, 18.4, 18.2, –4.2, –4.6, –5.0, –5.1; MS (EI) *m/z* (relative intensity) 471.3 (M^+, 5%), 456.3 ($[M–CH_3]^+$, 55%), 429.3 (100%); Anal. Calcd. for $C_{27}H_{45}NO_2Si_2$: C, 68.73; H, 9.61; N, 2.97. Found: C, 69.02; H, 9.76; N, 3.01.



(*S*,*R*)-22

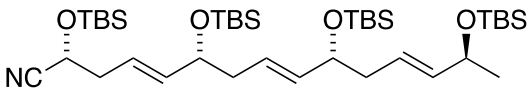
(2*S*,4*E*,6*R*,8*E*)-2,6-Di(*tert*-butyldimethylsilyloxy)-9-phenylnona-4,8-dienenitrile ((*S*,*R*)-22). From (*S*)-**1a** (70 mg, 0.19 mmol) and aldehyde **17b** (54 mg, 0.19 mmol) via General Procedure A was obtained (*S*,*R*)-**22** (79 mg, 96% yield, *E*/*Z* >95:5) as a colorless liquid; $[\alpha]_D^{25}$ –6.7 (c 0.585, $CHCl_3$); IR (film) 2956, 2930, 2896, 2857, 2234, 1472, 1362, 1256, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.16 (m, 5H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.21 (ddd, *J* = 15.8, 7.2, 7.2 Hz, 1H), 5.76-5.61 (m, 2H), 4.41 (dd, *J* = 6.2, 6.2 Hz, 1H), 4.26-4.21 (m, apparent q, *J* = 6.1 Hz, 1H), 2.58-2.42 (m, 2H), 2.40 (m, apparent t, *J* = 7.0 Hz, 2H), 0.91 (s, 9H), 0.90 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H), 0.06 (s, 3H),

0.05 (s, 3H); ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 138.8, 137.8, 132.5, 128.7, 127.2, 126.8, 126.2, 122.2, 119.8, 72.9, 62.5, 42.4, 39.4, 26.1, 25.7, 18.5, 18.3, –4.2, –4.6, –4.9, –5.1; MS (ESI) *m/z* (relative intensity) 471.2 (M^+, 5%), 489.05 ($[M+NH_4]^+$, 100%); HRMS (ESI-TOF) Calcd. for $C_{27}H_{45}NNaO_2Si_2$ ($[M+Na]^+$): 494.2887, Found: 494.2860.



24a

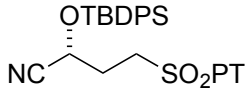
(2*R*,4*E*,6*R*,8*E*,10*S*)-2,6,10-Tri(*tert*-butyldimethylsilyloxy)-undeca-4,8-dienenitrile (24a). From nitrile **20a** (155 mg, 0.419 mmol) via General Procedure B was obtained aldehyde **20b** (125 mg, 80.1% yield) as a colorless oil. From (*R*)-**1a** (57 mg, 0.14 mmol) and **20b** (57.3 mg, 0.154 mmol) via General Procedure A was obtained **24a** (64 mg, 83% yield) as a colorless liquid; $[\alpha]_D^{26}$ +9.3 (c 0.69, $CHCl_3$); IR (film) 2956, 2930, 2858, 2238, 1472, 1462, 1362, 1256, 1149 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (dd, *J* = 15.4, 5.0 Hz, 1H), 5.61-5.43 (m, 2H), 5.47 (dd, *J* = 15.4, 4.7 Hz, 1H), 4.41 (dd, *J* = 6.5, 6.3 Hz, 1H), 4.30-4.21 (m, 1H), 4.15-4.08 (m, 1H), 2.55-2.41 (m, 2H), 2.27-2.14 (m, 2H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 18H), 0.18 (s, 3H), 0.14 (s, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 139.0, 138.8, 137.5, 124.8, 122.0, 121.9, 119.8, 72.9, 72.8, 69.4, 62.4, 62.3, 41.5, 39.4, 26.1, 25.7, 24.8, 18.4, 18.3, –4.1, –4.3, –4.5, –4.6, –4.9, –5.1; MS (ESI) *m/z* (relative intensity) 571.01 ($[M+NH_4]^+$, 62%), 354.10 (100%); HRMS (ESI-TOF) Calcd. for $C_{29}H_{59}NNaO_3Si_3$ ($[M+Na]^+$): 576.3701, Found: 576.3714.



25

(2*R*,4*E*,6*R*,8*E*,10*R*,12*E*,14*S*)-2,6,10,14-Tetra(*tert*-butyldimethylsilyloxy)-pentadeca-4,8,12-trienenitrile (25). From nitrile **24a** (65 mg, 0.12 mmol) via General Procedure B was obtained aldehyde **24b** (52.6 mg, 80.4% yield) as a colorless oil. From (*R*)-**1a** (30 mg, 0.074 mmol) and **24b** (41 mg, 0.074 mmol) via General Procedure A was obtained **25** (45.8 mg, 84.8% yield) as a colorless liquid; $[\alpha]_D^{22}$ +9.0 (c 0.5, $CHCl_3$); IR (film) 2956, 2929, 2896, 2857, 2242, 1472, 1463, 1362,

1255, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (dd, *J* = 15.3, 5.1 Hz, 1H), 5.61-5.40 (m, 5H), 4.41 (dd, *J* = 6.4, 6.4 Hz, 1H), 4.29-4.20 (m, apparent quintet, 1H), 4.16-4.02 (m, 2H), 2.52-2.46 (m, apparent t, *J* = 6.4 Hz, 2H), 2.29-2.10 (m, 4H), 1.18 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.890 (s, 9H), 0.886 (s, 9H), 0.88 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H), 0.05-0.03 (m, 15H), 0.01 (s, 3H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 138.9, 137.2, 136.1, 126.0, 125.4, 122.1, 73.7, 73.0, 69.5, 62.3, 41.7, 39.5, 30.0, 26.2, 25.8, 24.8, 18.5, 18.3, –4.2, –4.5, –4.9, –5.0; MS (ESI) *m/z* (relative intensity) 755.13 ($[M+NH_4]^+$, 75%), 354.10 (100%); HRMS (ESI-TOF) Calcd. for $C_{39}H_{79}NNaO_4Si_4$ ($[M+Na]^+$): 760.4984, Found: 760.4997.



(*R*)-**1b**

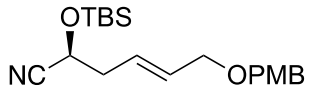
(*R*)-2-((*tert*-Butyldiphenylsilyl)oxy)-4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)butanenitrile ((*R*)-1b). To a solution of cyanohydrin (*R*)-**15a** (0.300 g, 1.15 mmol) in CH_2Cl_2 (13.0 mL) was added imidazole (0.195 g, 2.87 mmol) and *tert*-butyldiphenylsilyl chloride (0.45 mL, 1.72 mmol). After 48 h, the reaction mixture was partitioned between H_2O (10 mL) and CH_2Cl_2 (3 x 10 mL). The organic phase was washed with brine (3 mL) and dried over anhydrous Na_2SO_4. Concentration, gradient flash chromatography (petroleum ether to 40% EtOAc in petroleum ether), and heating at 60 °C under vacuum overnight to remove solvent afforded the *tert*-butyldiphenylsilyl ether (0.410 g, 71% yield) as a colorless waxy solid; $[\alpha]_D^{22}$ –19.2 (*c* 0.640, $CHCl_3$); IR (film) 3072, 2958, 2932, 2893, 2859, 1597, 1500, 1472, 1427, 1418, 1389, 1362, 1245, 1113, 1015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71-7.65 (m, 4H), 7.59-7.52 (m, 3H), 7.52-7.44 (m, 3H), 7.43-7.35 (m, 5H), 4.53 (dd, apparent t, *J* = 5.9 Hz, 1H), 3.54 (ddd, *J* = 14.0, 7.2, 6.8 Hz, 1H), 3.45 (ddd, *J* = 14.0, 7.2, 6.8 Hz, 1H), 2.45-2.32 (m, 2H), 1.11 (s, 9H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.5, 136.0, 135.9, 133.6, 131.6, 131.2, 130.65, 130.64, 130.3, 130.0, 128.22, 128.16, 123.8, 118.8, 61.5, 35.4, 28.1, 26.8, 19.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{27}H_{29}N_5OSSiNa$ 522.1760; Found 522.1759. Combustion analysis was not performed due to possible decomposition. Enantiomeric excess was measured by HPLC of product (*R*)-**1b** after the next step.

To a solution of the *tert*-butyldiphenylsilyl ether obtained above (0.369 g, 0.738 mmol) in EtOH (95%, 9.0 mL) at 0 °C was added ammonium molybdate tetrahydrate (0.027 g, 0.022 mmol) and H_2O_2 (30% wt. aq., 0.84 mL, 7.38 mmol). The reaction mixture was allowed to warm to room temperature. After 42 h, the reaction mixture was diluted with EtOAc (6 mL) and H_2O (6 mL), concentrated to remove EtOH, and partitioned between H_2O (10 mL) and EtOAc (3 x 10 mL). The organic phase was washed with brine (3 mL) and dried over anhydrous Na_2SO_4. Concentration, gradient flash chromatography (petroleum ether to 40% EtOAc in petroleum ether), and heating at 60 °C under vacuum overnight to remove solvent afforded (*R*)-**1b** (0.359 g, 91% yield, 94% ee) as a colorless waxy solid; mp 39-43 °C; IR (film) 3073, 2960, 2933, 2860, 1591, 1498, 1472, 1428, 1343, 1150, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71-7.67 (m, 6H), 7.65-7.59 (m, 3H), 7.53-7.42 (m, 6H), 4.59 (dd, apparent t, *J* = 5.1 Hz, 1H), 4.03 (ddd, *J* = 14.8, 10.4, 5.2 Hz, 1H), 3.90 (ddd, *J* = 14.8, 10.4, 5.2 Hz, 1H), 2.50-2.36 (m, 2H), 1.13 (s, 9H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.1, 135.9, 135.8, 132.9, 131.8, 131.1, 130.91, 130.87, 130.8, 130.0, 128.4, 128.3, 125.0, 117.9, 60.7, 51.6, 29.5, 26.8, 19.4; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{27}H_{29}N_5O_3SSiNa$ 554.1658; Found 554.1657; Anal. Calcd for $C_{27}H_{29}N_5O_3SSi$: C, 60.99; H, 5.50; N, 13.17. Found: C, 60.85; H, 5.61; N, 13.03. Enantiomeric excess was measured by HPLC on a Chiralcel OD-H column (gradient elution from 0% to 40% *i*-PrOH in hexane over 40 min, 1 mL/min), retention times: t_r 27.0 min (major (*R*)-isomer), t_r 28.1 min (minor (*S*)-isomer). For (*R*)-**1b** (>99% ee), $[\alpha]_D^{24}$ –8.76 (*c* 0.525, $CHCl_3$) (see below).

Alternate Procedure for Enantiopure (*R*)-1b. To a solution of enantiopure (*R*)-**1a** (4.16 g, 10.21 mmol) in MeOH (438 mL) and H_2O (73 mL) was added $TsOH{\cdot}H_2O$ (11.66 g, 61.30 mmol). After 71 h, the reaction mixture was diluted with EtOAc (100 mL), concentrated to remove MeOH, and partitioned between saturated aq. $NaHCO_3$ (50 mL) and EtOAc (3 x 100 mL). The organic phase was washed with brine (30 mL), and dried over anhydrous Na_2SO_4. Concentration and gradient flash chromatography (petroleum ether to 40% EtOAc in petroleum ether) afforded cyanohydrin (*R*)-**1c** (2.98 g, 99% yield) as a colorless solid; mp 87–91 °C; $[\alpha]_D^{23}$ +12.0 (*c* 0.500, DMSO); IR (film) 3506, 2992, 2971, 2922, 1498, 1462, 1343, 1244, 1145, 1079 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 7.71-7.63 (m, 5H), 4.66 (ddd, apparent q, *J* = 6.1 Hz, 1H), 4.43 (d, *J* = 6.1 Hz, 1H),

3.82-3.76 (m, 2H), 2.42-2.30 (m, 2H); $^{13}C\{1H\}$ NMR (125 MHz, CD_3CN) δ 154.3, 134.2, 132.6, 130.5, 126.9, 120.2, 59.2, 52.6, 28.8; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{11}H_{11}N_5O_3SNa$ 316.0480; Found 316.0478. Reprotection of (*R*)-**1c** with TBSCl and optical rotation measurement ($[\alpha]_D^{22}$ +23.8 (*c* 0.500, $CHCl_3$) showed no significant loss of enantiopurity, as confirmed by HPLC analysis of product (*R*)-**1b** after the next step.

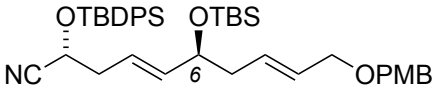
To a solution of cyanohydrin (*R*)-**1c** (1.83 g, 6.24 mmol) in CH_2Cl_2 (70 mL) was added imidazole (1.06 g, 15.60 mmol) and *tert*-butyldiphenylsilyl chloride (2.43 mL, 9.36 mmol). After 45 h, the reaction mixture was partitioned between H_2O (100 mL) and CH_2Cl_2 (3 x 100 mL). The organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Concentration, gradient flash chromatography (petroleum ether to 40% Et_2O in petroleum ether), and heating at 60 °C under vacuum overnight to remove solvent afforded (*R*)-**1b** (3.27 g, 98% yield, >99% ee) as a colorless waxy solid; $[\alpha]_D^{24}$ –8.76 (*c* 0.525, $CHCl_3$). Enantiomeric excess was measured by HPLC on a Chiralcel OD-H column (gradient elution from 0% to 40% *i*-PrOH in hexane over 40 min, 1 mL/min), retention times: t_r 27.0 min (major (*R*)-isomer), t_r 28.1 min (minor (*S*)-isomer).



27a

(*S*,*E*)-2-((*tert*-Butyldimethylsilyl)oxy)-6-((4-methoxybenzyl)oxy)hex-4-enenitrile (27a). To a solution of sulfone (*S*)-**1a** (2.86 g, 7.03 mmol) in DME (>99%, anhydrous, 156 mL) at –60 °C was added KHMDS (0.5 M in toluene, 16.86 mL, 8.43 mmol). After 1.5 h, aldehyde **26**[51] (1.90 g, 10.54 mmol) in DME (>99%, anhydrous, 53 mL) was cooled to –60 °C and slowly added by cannula over 10 min. After 4.5 h at –60 °C, the reaction was quenched with saturated aq. NH_4Cl (30 mL) and allowed to warm to room temperature over 30 min, then partitioned between H_2O (20 mL) and EtOAc (3 x 50 mL). The organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Concentration gave a mixture of *E* and *Z* isomers (*E*/*Z* 87:13), and gradient flash chromatography (petroleum ether to EtOAc) afforded **27a** (2.18 g, 86% yield, *E*/*Z* 90:10) as a colorless oil. Careful radial chromatography (petroleum ether/EtOAc) gave a slightly enriched ratio of the minor (*Z*)-isomer (*E*/*Z* 65:35), followed by the major (*E*)-isomer (*E*/*Z* 98:2). The *E*/*Z*

ratios were determined by ^{1}H NMR and confirmed by GC-HRMS. For (*E*)-**27a** (*E*/*Z* 98:2): $[\alpha]_D^{22}$ –16.6 (*c* 0.500, $CHCl_3$); IR (film) 2955, 2931, 2898, 2858, 1613, 1513, 1465, 1362, 1302, 1251, 1173, 1112, 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.84-5.68 (m, 2H), 4.45 (s, 2H), 4.44 (dd, apparent t, *J* = 6.5 Hz, 1H), 4.01-3.98 (m, 2H), 3.80 (s, 3H), 2.60-2.49 (m, 2H), 0.92 (s, 9H), 0.19 (s, 3H), 0.14 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 159.3, 132.4, 130.4, 129.5, 125.7, 119.7, 113.9, 71.9, 69.9, 62.1, 55.4, 39.4, 25.6, 18.2, –5.0, –5.2; HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{20}H_{31}NO_3Si$ 361.2073; Found 361.2081; Anal. Calcd for $C_{20}H_{31}NO_3Si$: C, 66.44; H, 8.64; N, 3.87. Found: C, 66.66; H, 8.75; N, 3.83. For (*Z*)-**27a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (d, *J* = 8.8 Hz, 2H), 5.85 (ddd, *J* = 11.4, 6.3, 6.3 Hz, 1H), 5.66-5.58 (m, 1H), 4.41 (dd, apparent t, *J* = 6.5 Hz, 1H), 4.07-4.04 (m, 2H), 3.81 (s, 3H), 0.90 (s, 9H), 0.17 (s, 3H), 0.12 (s, 3H), other peaks were not resolved; ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 159.4, 131.4, 130.2, 129.6, 125.4, 119.7, 113.9, 72.2, 65.4, 61.8, 34.8, 18.17, –5.1, other peaks were not resolved. For the *E*/*Z* mixture: GC-HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{20}H_{31}NO_3Si$ 361.2073: retention times: t_r 22.5 min (27% minor (*Z*)-isomer, Found 361.2049), t_r 22.9 min (73% major (*E*)-isomer, Found 361.2065).



28

(2*R*,4*E*,6*S*,8*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-((*tert*-butyldiphenylsilyl)oxy)-10-((4-methoxybenzyl)oxy)deca-4,8-dienenitrile (28). To a solution of nitrile **27a** (0.256 g, 0.71 mmol, *E*/*Z* 89:11) in toluene (18 mL) at –78 °C was added DIBAL-H (1M in heptane, 1.06 mL, 1.06 mmol) dropwise. After 4 h, MeOH (2 mL) was slowly added to quench remaining DIBAL-H and the reaction mixture was allowed to warm to room temperature. After 1 h, the reaction mixture was diluted with Et_2O (100 mL) and washed repeatedly with dilute aq. tartaric acid (0.1 mM, 10 x 700 mL, 1 equiv), adding brine (50 mL) to each wash. The organic phase was then washed with H_2O (2 x 10 mL), then brine (10 mL), and dried over anhydrous Na_2SO_4. Concentration afforded the crude aldehyde **27b** (0.204 g, 79% yield) as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (d, *J* = 1.5 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.70-5.67 (m, 2H), 4.42 (s, 2H), 4.02 (ddd, *J* = 7.0, 5.5, 1.5 Hz, 1H), 3.96-3.93 (m, 2H), 3.81 (s, 3H), 2.50-2.33 (m, 2H), 0.92 (s,

9H), 0.08 (s, 3H), 0.07 (s, 3H). The minor (*Z*)-isomer peaks were not resolved. The aldehyde **27b** was stored frozen in benzene (ca. –5 °C) and used in the subsequent step without further purification.

To a solution of sulfone (*R*)-**1b** (0.595 g, 1.12 mmol) in THF (25 mL) at –78 °C was slowly added KHMDS (0.5 M in toluene, 2.13 mL, 1.06 mmol) by syringe over 5 min. After 1 h, a solution of aldehyde **27b** (0.204 g, 0.56 mmol) in THF (2.8 mL) was slowly added by syringe over 5 min. After 5 h, the reaction was quenched with saturated aq. NH_4Cl (5 mL) and H_2O (5 mL), allowed to warm to room temperature over 30 min, and extracted with EtOAc (3 x 20 mL). The organic phase was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Concentration and gradient flash chromatography (petroleum ether to 40% EtOAc in petroleum ether) afforded unreacted sulfone (*R*)-**1b** (57% recovery without loss of enantiopurity) and **28** (0.246 g, 52% yield over two steps, *E*,*E*/*E*,*Z* 88:12, *R*,*S*/*R*,*R* 97:3) as a colorless oil. No minor (*Z*,*E*)- or (*Z*,*Z*)-isomers were observed by ^1H or ^{13}C NMR. The isomers could be enriched by careful radial chromatography (40% Et_2O in petroleum ether) with the minor (*E*,*Z*)-isomer eluting before the major (*E*,*E*)-isomer and their ratios were determined by ^1H NMR. The *R*,*S*/*R*,*R* diastereomers were inseparable by radial/flash chromatography and their ratios were determined by ^1H NMR. For (*R*,*E*,*S*,*E*)-**28** (*E*,*E*/*E*,*Z* 94:6, *R*,*S*/*R*,*R* 97:3): $[\alpha]_D^{22}$ +4.74 (*c* 1.27, $CHCl_3$); IR (film) 3072, 3000, 2932, 2895, 2857, 1613, 1513, 1471, 1428, 1362, 1249, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71-7.69 (m, 2H), 7.67-7.64 (m, 2H), 7.50-7.38 (m, 6H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.72-5.56 (m, 4H), 4.42 (s, 2H), 4.33 (dd, *J* = 7.0, 4.8 Hz, 1H), 4.14 (ddd, *J* = 6.0, 6.0, 4.4 Hz, 1H), 3.95-3.93 (m, apparent d, *J* = 5.4 Hz, 2H), 3.80 (s, 3H), 2.52 (ddd, *J* = 13.2, 7.2, 4.8 Hz, 1H), 2.36 (ddd, *J* = 13.6, 5.8, 4.8 Hz, 1H), 2.29-2.18 (m, 2H), 1.10 (s, 9H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 138.9, 135.9, 135.8, 132.2, 131.6, 130.7, 130.6, 130.5, 130.4, 129.5, 129.3, 128.13, 128.11, 121.7, 119.1, 113.9, 72.5, 71.7, 70.7, 63.3, 55.4, 41.5, 39.0, 26.8, 26.0, 19.4, 18.4, –4.2, –4.7; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{40}H_{55}NO_4Si_2Na$ 692.3567; Found 692.3571; Anal. Calcd for $C_{40}H_{55}NO_4Si_2$: C, 71.70; H, 8.27; N, 2.09. Found: C, 71.77; H, 8.26; N, 2.23. For (*R*,*E*,*S*,*Z*)-**28**, ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (m, apparent d, *J* = 6.2 Hz, 2H), other peaks were not resolved.

From a different run under conditions leading to an undesired epimerization (reaction mixture from DIBAL-H reduction of **27a** was refluxed with saturated aq. Rochelle's salt), was obtained a sample enriched in (*R*,*E*,*R*,*E*)-**28** (*R*,*S*/*R*,*R* 73:27); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 9H), 0.02 (s, 3H), other peaks were not resolved; ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 139.0, 135.9, 135.8, 130.3, 129.2, 121.7, 72.7, 70.6, 63.0, 41.4, 39.0, 26.8, 26.0, 18.3, –4.7, other peaks were not resolved.

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Supporting Information. ^{1}H and ^{13}C NMR spectra for new compounds, data on enantiomer ratios and configuration assignments.

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