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# Advances and Setbacks in the Total Synthesis of the Fungal Metabolite Curvicollide C: Synthesis and Elaboration of Non-Aldol Stereotriads from Gosteli-Type Allyl Vinyl Ethers

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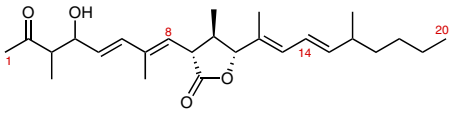
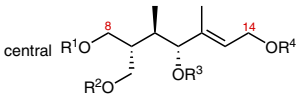
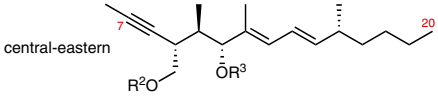


**curvicollide C**:
fungal metabolite; abs. and rel. config. unknown; unique constitution
building block synthesis:

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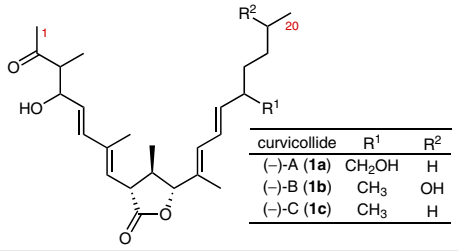
**Abstract** Advances and setbacks are reported in regard to the asymmetric total synthesis of the fungal metabolite curvicollide C relying on a synthetic strategy that exploits non-aldol stereotriads as chiral building blocks. A catalytic asymmetric Gosteli–Claisen rearrangement, a two-step aldehyde-to-alkyne-homologation, and a Julia–Kocienski olefination served as key C/C-connecting transformations.

**Key words** antifungal agents, total synthesis, Claisen rearrangement, Michael addition, chiral auxiliaries, ozonolysis

Fungicides are chemical entities that are used for the management of fungal infections of humans, animals, and plants. Invasive fungal infections are life-threatening for critically ill or immunocompromised patients. The limited number of antifungal agents in concert with the emergence and spread of drug-resistant *Candida* and *Aspergillus* strains constitute the need for the development of fungicides with new modes of action.[1–5] However, fungal-selective eukaryotic cellular targets are more challenging to identify compared to prokaryotes or viruses.[6] The development of new classes of antifungal metabolites from natural sources could provide new opportunities for the therapeutic treatment of fungal infections.[7]

In 2004, Gloer and collaborators reported antifungal activity of an extract of fermentation cultures of *Podospora curvicolla* against *Aspergillus flavus* and *Fusarium verticillioides*.[8] From the fungicidal crude extract (3.3 g), the linear polyketides curvicollide A (**1a**, 6.5 mg), B (**1b**, 2.1 mg), and C (**1c**, 3.0 mg) were isolated. Curvicollide A (**1a**) demonstrated antifungal activity against *A. flavus* and *F. verticilloides* in disk assays. Because of the limited availability of curvicollide B (**1b**) and C (**1c**), their respective antifungal activities were not tested by Gloer et al. The interpretation of the results of NMR experiments revealed the molecular constitution of **1a–c** and, in part, the relative configuration of **1a** (Figure 1). The relative configuration of the γ-lactone moiety in **1b** and **1c** was only assigned in analogy. The constitution of the γ-lactone structural element of **1a–c** deviates from the regular polyketide architecture. Gloer and collaborators suggested the condensation of two polyketide units by carbon–carbon bond formation in order to explain the curvicollide architecture. A biosynthetic pathway involving a Favorski-type rearrangement of regular linear polyketide precursors could also account for the formation of the unique γ-lactone structural element featuring a non-aldol stereotriad.[9]

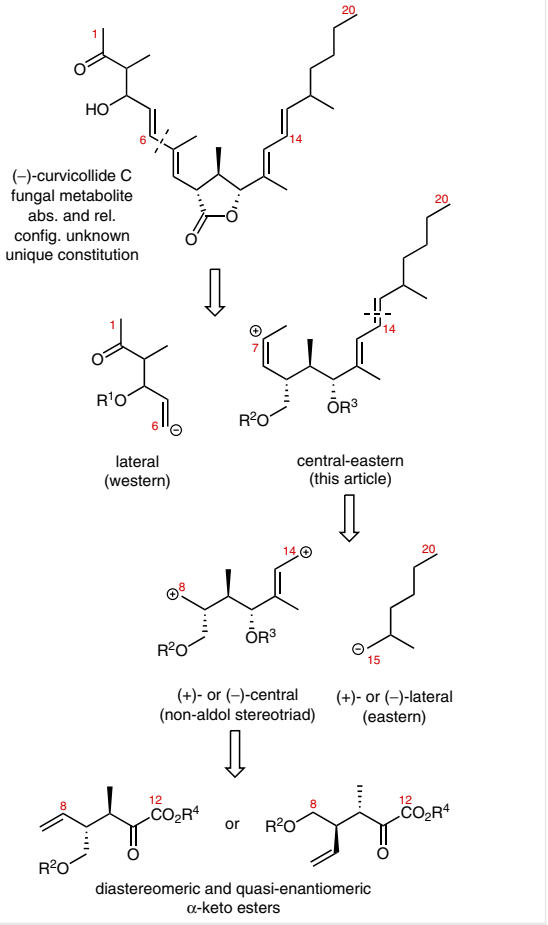


| curvicollide | $R^1$ | $R^2$ |
|---|---|---|
| (–)-A (**1a**) | $CH_2OH$ | H |
| (–)-B (**1b**) | $CH_3$ | OH |
| (–)-C (**1c**) | $CH_3$ | H |

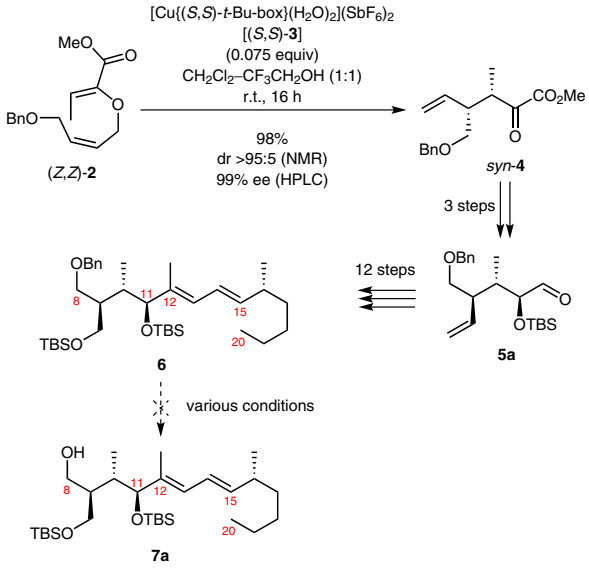
**Figure 1** Reported structures of the fungal metabolites curvicollide A–C (*Podospora curvicolla*)

The mycoparasite *Podospora curvicolla* was initially collected from a sclerotium of an *Aspergillus flavus* species found in Illinois (USA).

The unprecedented molecular architecture of the curvicollides **1a–c** could give rise to a creative process-like interaction between method development and target-oriented synthesis. Furthermore, an asymmetric total synthesis would enable the completion of the structural assignment,




**Scheme 1** Modular central-to-lateral synthetic strategy to curvicollide C. The curvicollide numbering system is used for all fragments and building blocks throughout the article.




**Scheme 2** Previous effort aimed at the total synthesis of (–)-curvicollide A

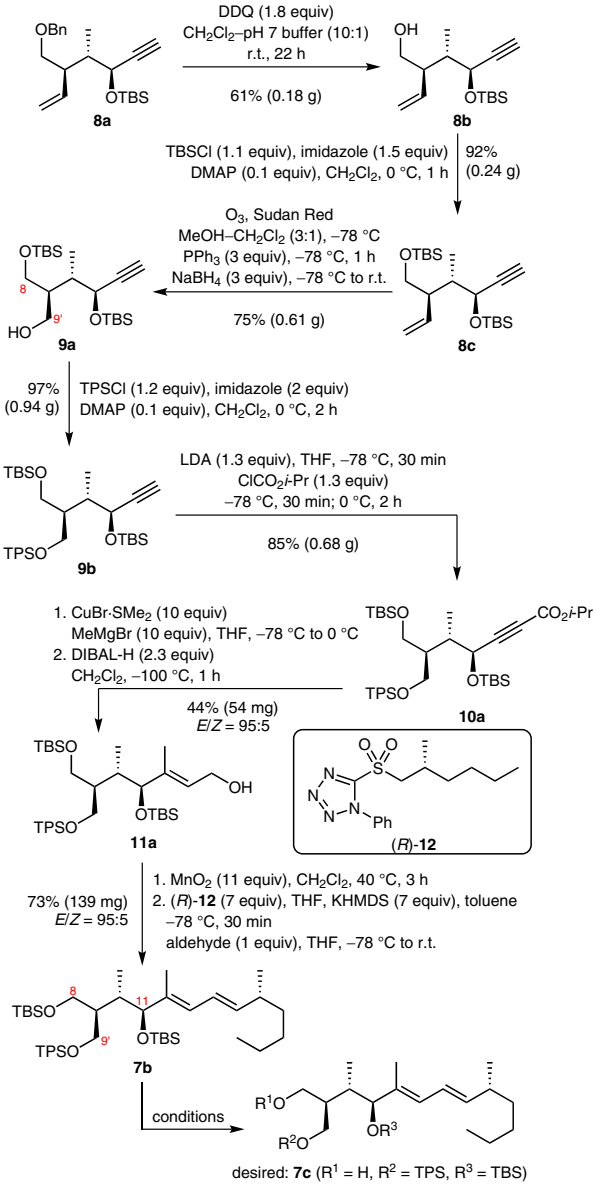
and drive the further evaluation of the antifungal properties. Thus, we have initiated a research project aimed at the total synthesis of (–)-curvicollide C (**1c**).

Aiming to elucidate the absolute configuration of (–)-curvicollide C (**1c**) by total synthesis, we decided to pursue a modular central-to-lateral strategy (Scheme 1). Thus, a suitably elaborated central building block was required in order to assemble from the central to the lateral in a convergent manner. We felt comfortable implementing this modular strategy because it enables redeployment of the required stereodiverse synthesis to the smaller lateral building blocks. In further developing the central-to-lateral strategy toward (–)-curvicollide C (**1c**), we recognized the opportunity to access central building blocks that are characterized by the non-aldol type stereotriad starting from β,γ-branched δ,ε-unsaturated α-keto esters.[10]

In this article, our efforts to implement the central-to-lateral synthetic strategy are described. We will delineate the successful asymmetric synthesis of central and lateral building blocks as well as their coupling. We will further outline initial advances and ultimate setbacks in the elaboration of the central eastern building block.

We previously reported the synthesis of the α-keto ester *syn*-**4** by catalytic asymmetric Claisen rearrangement of the Gosteli-type allyl vinyl ether (*Z*,*Z*)-**2** (Scheme 2).[11] Post-rearrangement transformations delivered aldehyde **5a** that was converted into the C8–C20 building block **6**. In executing the projected sequence from **6** to curvicollide C (**1c**), a major obstacle was anticipated in the chemoselective cleavage of the benzyl-protecting group in the presence of the diene moiety. Hence, we avoided reductive conditions and turned our attention to the application of Lewis acids or oxidants. However, Lewis acids (e.g., $BCl_3{\cdot}SMe_2$,[12] $BCl_3$,[13] $FeCl_3$-[14]) triggered cleavage of both silyl ethers whereas subjecting compound **6** to DDQ-induced cleavage[15] of the allylic silyl ether at C11.

Notwithstanding this setback, we continued to favor the convergent central-to-lateral approach, wherein the lateral aldol segment would be connected to a larger central-eastern segment at a late stage of the synthetic sequence. Toward this end, and intending to circumvent the previously experienced hurdle, we set out to switch the critical protecting group at C8. Hence, the known enyne **8a**[11a] was reacted with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in a mixture of $CH_2Cl_2$ and aqueous buffer to yield the primary alcohol **8b** in moderate yield (61% isolated yield, 0.18 g isolated mass, Scheme 3). Subsequent silyl ether formation proceeded uneventful and delivered the enyne **8c** (92%). Synthesis of the desired non-aldol stereotriad was completed by chemoselective ozonolysis of the




| Entry | Conditions | $R^1$ | $R^2$ | $R^3$ | Yield |
|---|---|---|---|---|---|
| 1 | $NH_4F$ (100 equiv), MeOH, r.t., 24 h | TBS | TPS | TBS | 99% |
| 2 | HF-pyridine, $CH_2Cl_2$, 0 °C, 1 h | H | H | H | 79% |
| 3 | TBAF (1.1. equiv), THF, r.t., 16 h | H | TPS | H | 72% |
| 4 | Oxone (1.1 equiv), MeOH, 0 °C, 4 h | H | TPS | H | 60% |

**Scheme 3** Successful synthesis of the building block **7b** and failed attempts to access the alcohol **7c** by selective cleavage of the TBS protecting group at C8

double bond with reductive workup and in situ reduction to deliver the alcohol **9a** (75%). In order to allow for chemical differentiation between the primary hydroxyl groups at C8 and C9′ at a later stage of the synthesis, we decided to introduce a *tert*-butyldiphenylsilyl (TPS)-protecting group.[16] Thus, subjecting the alcohol **9a** to standard conditions for silyl ether formation afforded the tris-silyl ether **9b** (97%). We next concentrated our efforts on synthesizing the *E*-configured allylic alcohol **11a**. Toward this end, terminal alkyne **9b** was treated with LDA and isopropyl chloroformate to give the alkynoate **10a** in good yield (85%). Exposure of **10a** to a large excess of freshly prepared copper(I) bromide dimethyl sulfide complex and methylmagnesium bromide in THF at –78 °C delivered upon warming to 0 °C the corresponding alkenoate.[17,18] Subsequent reduction of the alkenoate with an excess of diisobutylaluminum hydride (DIBAL-H) in THF at low temperature provided the allylic alcohol **11a** (44% from **10a**, *E*/*Z* = 95:5). Having completed the assembling of the central building block **11a**, efforts were directed to couple the central with the eastern lateral building block by installation of the C14/C15 double bond. Hence, the allylic alcohol **11a** was oxidized with manganese dioxide at elevated temperature.[19] Subsequent Julia–Kocienski olefination[20] using a large excess of the known sulfone (*R*)-**12**[11a] and potassium bis(trimethylsilyl)amide in THF yielded the *E*,*E*-configured diene **7b** (79% from **11a**, *E*/*Z* = 95:5). Selective cleavage of the primary TBS ether[21] at C8 in the presence of the primary TPS ether at C9′ and the secondary TBS ether at C11 was then required in order to afford the desired alcohol **7c**. To our dismay, however, none of the conditions probed enabled the differentiation of the primary and the secondary TBS ether. Exposure of the tris-silyl ether **7b** to ammonium fluoride in methanol at ambient temperature led to no conversion (Scheme 3, entry 1). Using hydrogen fluoride pyridine in dichloromethane at 0 °C triggered rapid cleavage of all silyl ethers (entry 2). Subjecting compound **7b** to tetra-*n*-butylammonium fluoride in THF at room temperature or to Oxone in methanol[22] at 0 °C resulted in the cleavage of the primary as well as the allylic secondary TBS ethers (entries 3 and 4). This outcome again illustrates the pronounced susceptibility of the allylic silyl ether for cleavage under various conditions, and evaluation of alternative protecting group patterns was inevitable.

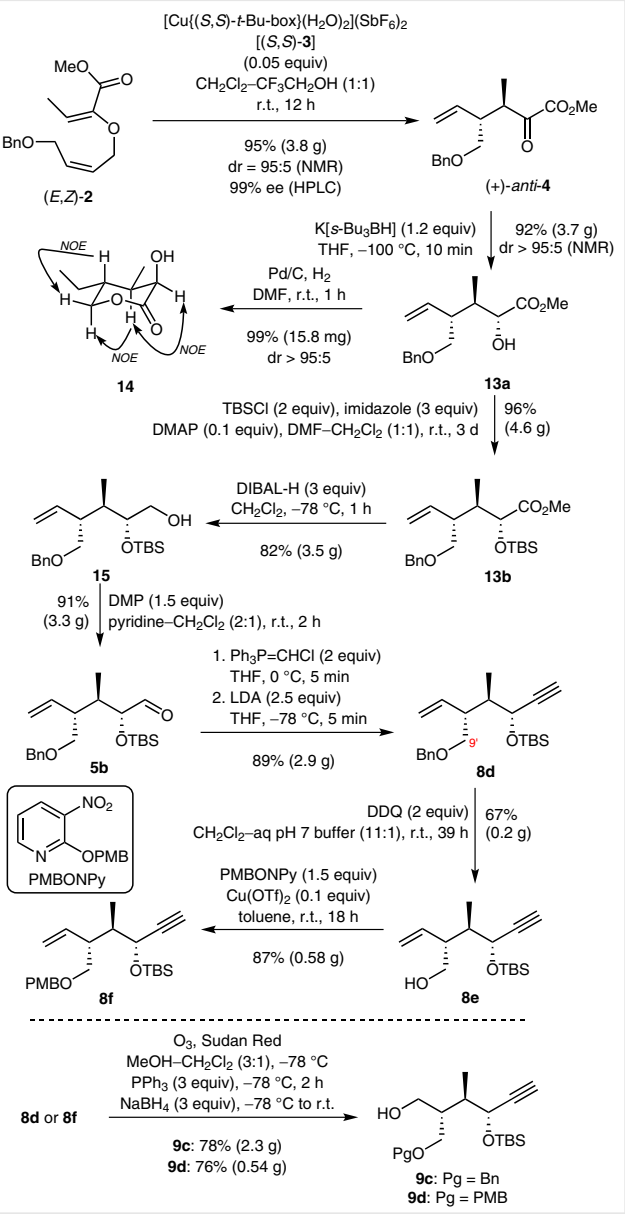
An alternative route to non-adol-type building blocks embarked from the known Gosteli-type allyl vinyl ether (*E*,*Z*)-**2** (Scheme 4).[11] Catalytic asymmetric Gosteli–Claisen rearrangement (CAGC) of (*E*,*Z*)-**2** using the Evans-type copper(II) bis(oxazoline) Lewis acid (*S*,*S*)-**3** delivered the α-keto ester *anti*-**4** in high yield and stereoselectivity on gram scale (98%, dr = 95:5, 95% ee). Importantly, a faster turnover was observed when the catalyzed rearrangement was run in an equal volume mixture of $CH_2Cl_2$ and 2,2,2-trifluoroethanol instead of pure $CH_2Cl_2$ as reported previously.[23] Notably, CAGC of Gosteli-type allyl vinyl ethers analogous to (*E*,*Z*)-**2** but equipped with different silyl protecting groups were less diastereoselective (*t*-BuPh$_2$Si: dr = 83:17; *t*-BuMe$_2$Si: dr = 80:20); the presence of a PMB instead of the Bn protecting group turned out to be incompatible with the Lewis acidity of the catalyst **3**. Highly diastereoselective reduction of the α-keto ester (+)-*anti*-**4** with K-Selectride delivered the α-hydroxy ester **13a** as a single diastereomer (92%).[24] Hydrogenolysis, hydrogenation, and lactonization

in a single operation delivered the δ-lactone **14** (99%); NOE studies on **14** support the assignment of the relative configuration of the non-aldol stereotriad of **15a**. Subsequent TBS protection of the secondary hydroxyl group (94%), reduction of the ester to the alcohol with diisobutylaluminum hydride (82%), and oxidation using the Dess–Martin periodinane (DMP)[25] (91%) all proceeded uneventful to yield the aldehyde **5b**. Aldehyde-to-alkyne homologation was accomplished by a two-step procedure. Exposure of **5b** to triphenylphosphinechloromethylene, prepared from chloromethyltriphenylphosphonium chloride and *n*-BuLi, delivered the corresponding vinylic chloride.[26] Subsequent treatment of the vinylic chloride with lithium diisopropylamide triggered β-elimination to yield the desired alkyne **8d** (88%).[27] Attempted dibromomethylenation of **5b** according to Corey and Fuchs trigged cleavage of the TBS ether and partial epimerization.[28] Application of the Ohira–Bestmann protocol led to decomposition of **5b**.[29]

The setbacks delineated in Scheme 2 prompted us to consider alternatives for the benzyl-protecting group at C9′ of the enyne **8d**. After some optimization, conditions for the oxidative removal of the benzyl-protecting group using a two-fold excess of DDQ in a 11:1 mixture of $CH_2Cl_2$ and aqueous pH 7 buffer served to prepare the alcohol **8e** in moderate yield (67%). Exposure of **8e** to 2-(4-methoxybenzyloxy)-3-nitropyridine (PMBONPy) according to Mukaiyama using copper(II) triflate instead of trimethylsilyl triflate delivered the *p*-methoxybenzyl ether **8f** in good yield (87%).[30] Ozonolysis of compounds **8d**,**f** with reductive workup and in situ reduction provided the alcohols **9c**,**d** (80%, 75%), respectively.

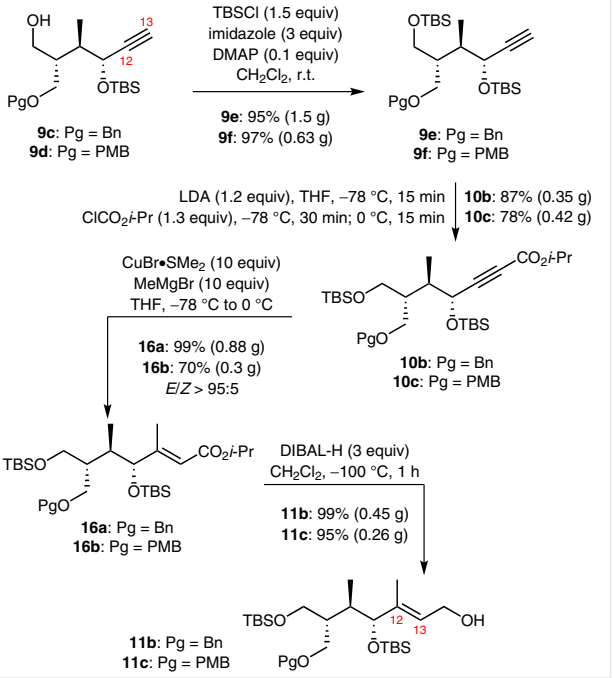
With the non-aldol stereotriad building blocks **9c**,**d** in hand, we turned our attention to the construction of the trisubstituted C12/C13 double bond (Scheme 5). The required chemistry had been established for the purpose of the synthesis of the *E*-configured allylic alcohol **11a** from the alkyne **9b** (Scheme 3). Thus, formation of the bis-TBS ether delivered the tris-protected alkynes **9e**,**f** (95%, 98%). Subsequent lithiation and isopropoxycarbonylation yielded the alkynoates **10b**,**c** (87%, 78%), and methyl cupration finally provided the *E*-configured enoates **16a**,**b** (99%, 70%). The synthesis of the allylic alcohols **11b**,**c** was completed by DIBAL-H reduction of **16a**,**b**. Notably, compounds **11a** as well as **11b**,**c** represent differently protected *enantiomeric* building blocks that were synthesized from the *diastereomeric* α-keto esters *syn*- and *anti*-**4**.

Relying on the procedures used for the synthesis of **7b**, we next turned to the coupling of **11b**,**c** with both enantiomers of the eastern building block **12** (Scheme 6). Hence, $MnO_2$-mediated oxidation of the allylic alcohols **11b**,**c** was followed by Julia–Kocienski olefination with *S*- or *R*-configured sulfones **12** to deliver the *E*,*E*-dienes **7d**–**f** in fair yields (58–75%).



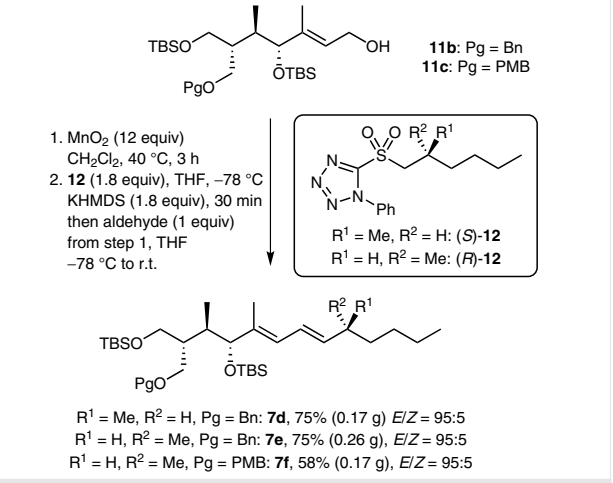

**Scheme 4** Asymmetric synthesis of non-aldol stereotriad building blocks **9c**,**d** based on catalytic asymmetric Claisen rearrangement of Gosteli-type allyl vinyl ether (*E*,*Z*)-**2**

The asymmetric synthesis of the sulfone (*S*)-**12** is depicted in Scheme 7.[31] (*S*)-3-Hexanoyl-4-isopropyloxazolidin-2-one (**17**) was subjected to sodium hexamethyldisilazide and methyl iodide to yield (*S*)-4-isopropyl-3-[(*S*)-2-methylhexanoyl]oxazolidin-2-one (**18**) in very good yield and with excellent diastereoselectivity (93%, dr >95:5).[32] Reductive cleavage and recovery of the auxiliary (91%) delivered the alcohol (–)-(*S*)-**19**[33] that was purified by distillation in very good yield (90%). The absolute configuration of the alcohol was assigned in accordance with the excepted empirical model for the stereochemical course of alkyla-

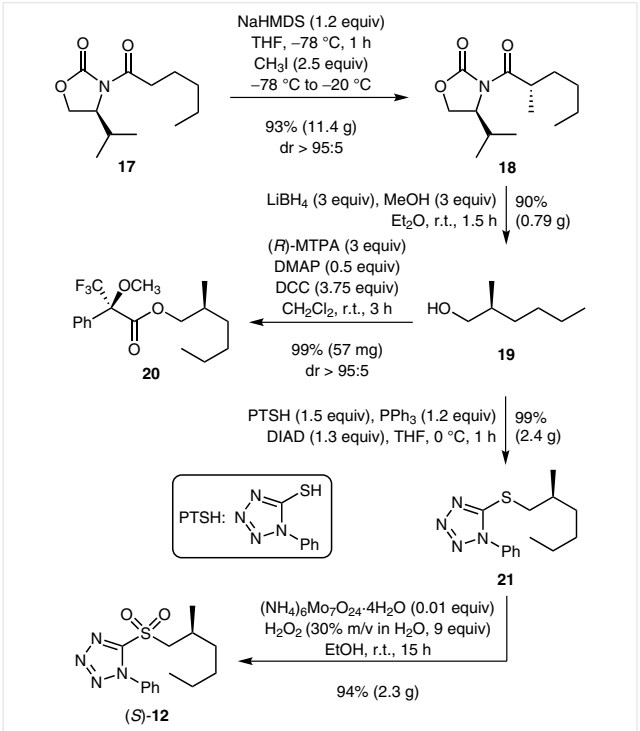



**Scheme 5** Elaboration of the non-aldol stereotriad building blocks **11b**,**c**. Detailed conditions refer to Pg = Bn and may vary for Pg = PMB; see experimental section for details.

tions controlled by Evans-type auxiliaries.[34] Mosher ester analysis[35] confirmed the high enantiomeric excess expected for (–)-(*S*)-2-methylhexan-1-ol (**19**). The synthesis of the sulfone (*S*)-**12** was completed by Mitsunobu reaction[36] of (–)-(*S*)-**19** with phenyltetrazole-5-thiol to deliver the sulfide **21**. Oxidation of compound **21** with $H_2O_2$ in the presence of catalytic amounts of ammonium heptamolybdate[37] finally afforded the desired eastern building block (*S*)-**12**.

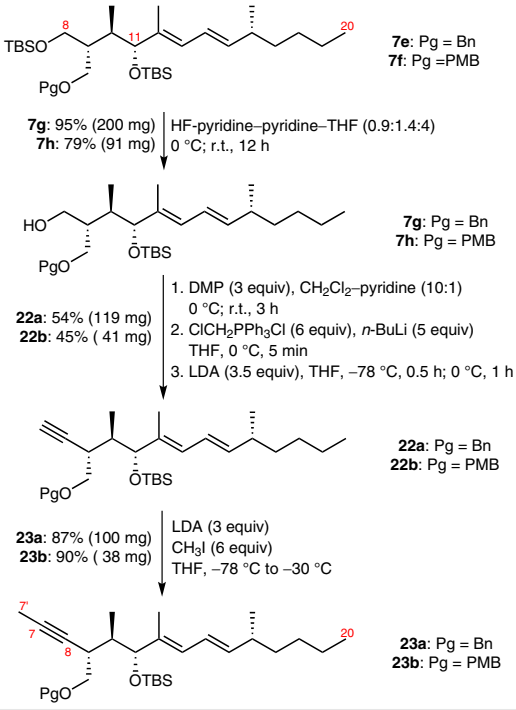



**Scheme 6** Coupling of the central and eastern building by Julia–Kocienski olefination; conditions refer to Pg = Bn and may vary for Pg = PMB; see experimental section for details.




**Scheme 7** Asymmetric synthesis of the sulfone (*S*)-**12**

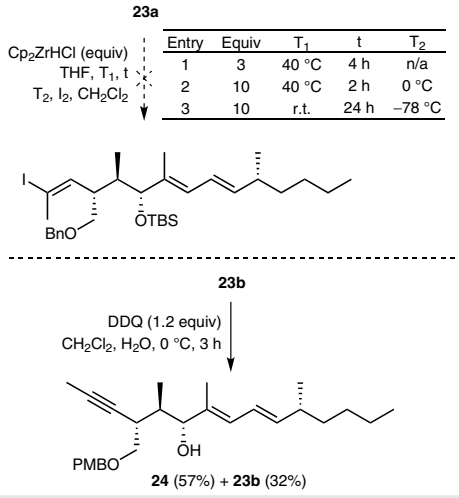
With compounds **7e**,**f** in hand, their elaboration to central eastern building blocks according to our initial planning was explored (Scheme 8). In order to attach the missing carbon atoms C7 and C7′ by alkynylation of a C8 aldehyde functionality, chemoselective cleavage of the primary silyl ether at C8 in the presence of the secondary but allylic silyl ether at C11 was required. Previous efforts including the use of HF-pyridine in $CH_2Cl_2$ had been futile (Scheme 3). However, adding pyridine afforded a distinct mixture of HF-pyridine, 'extra' pyridine, and $CH_2Cl_2$ that affected the desired cleavage of the primary silyl ether in very good yield (95%) for **7g** (Pg = Bn) and still acceptable yield (79%) for **7h** (Pg = PMB).[38] Subsequent alkynylation of the primary alcohols **7g**,**h** proceeded uneventful and was achieved by a sequence consisting of Dess–Martin oxidation,[25] chloromethylenation, and base-mediated elimination to deliver the alkynes **22a**,**b** in moderate overall yield (54%, 45%) and without notable epimerization at C9. The presence of the terminal alkyne functionality then allowed for the introduction of the C7′ methyl group.[39] Thus, upon treatment of compounds **22a**,**b** with an excess of lithium diisopropylamide and methyl iodide the dienynes **23a**,**b** were isolated in very good yields (87%, 90%).




**Scheme 8** Synthesis of the C7–C20 building blocks **23a**,**b** by chemoselective silyl ether cleavage and aldehyde-to-alkyne homologation

With the dienyne **23a** in hand, we proceeded to complete the synthesis of a central eastern building block. Our initial tactic for fragment coupling considered cross-coupling or Heck-type reaction for C7–C6 bond formation. Thus, we sought to convert the alkyne **23a** to the corresponding vinyl iodide using chloridobis(η$^5$-cyclopentadienyl)hydridozirconium according to Schwartz (Scheme 9).[40] However, no conversion was detected by TLC when subjecting compound **23a** to a small excess (3 equiv) of $Cp_2ZrHCl$ in $CH_2Cl_2$ at 40 °C for 4 hours. Using a large excess (10 equiv) of the Schwartz reagent at 40 °C triggered consumption of the starting material. Subsequent addition of iodine afforded an inseparable product mixture. NMR analysis of this mixture led us to conclude that the conversion of **23a** to the desired vinyl iodide was complicated by the competitive formation of two isomeric vinyl iodides as well as protodezirconation of the intermediate vinyl zirconium species. Two sets of characteristic vinylic $^1$H NMR multiplets indicated the intactness of the C12–C14 diene moiety. Some attempts were undertaken to bias the positional selectivity of the hydrozirconation. For instance, subjecting the dienyne **23a** to a large excess (10 equiv) of Schwartz's reagent in THF at ambient temperature required 24 hours for complete consumption of the starting material according to TLC analysis. Subsequent cooling to –78 °C and addition of iodine again delivered an inseparable product mixture. As an alternative to hydrozirconation, we briefly studied the palladium-catalyzed hydrostannation of the dienyne **23a**.[41]

Using catalytic amounts of bis(triphenylphosphine)palladium(II) dichloride and stoichiometric amounts of tri-*n*-butyltin hydride in different solvents and at different temperatures led to no conversion. At this point, we turned to the PMB-protected building block **23b** with the intent to construct the central lactone – or lactol – upstream to the further functionalization of the C7/C8 triple bond. However, and although expected otherwise,[42] the primary PMB ether at C9′ could not be cleaved using DDQ in buffered or non-buffered aqueous solutions. Once again, the allylic TBS ether at C11 was found to be very susceptible to different conditions for oxidative ether cleavage.[15] This constitutes a problem that, at that time, could not be solved in our hands.




**Scheme 9** Attempted hydrozirconation-iodination of **23a** and unexpected protecting group chemistry of **23b**

In conclusion, we have reported the asymmetric synthesis of various building blocks for the crucial non-aldol stereotriad that uniquely characterizes the curvicollides A–C. One key feature of our investigation includes the use of the catalytic asymmetric Gosteli–Claisen rearrangement for the synthesis of β,γ-branched δ,ε-unsaturated α-keto esters that serve as valuable chiral building blocks. A series of post-rearrangement transformations enabled multifaceted structural elaboration of these α-keto esters. In addition, *E*-diastereoselective alkynoate methyl cupration in combination with an *E*-diastereoselective Julia–Kocienski olefination enabled building block coupling and 1,3-diene formation. Finally, our studies revealed challenges associated with protecting group chemistry and functional group interconversion that currently are being addressed.

Unless otherwise stated, commercially available reagents, catalysts, and solvents were used as purchased. THF, $CH_2Cl_2$, MeCN, and $Et_2O$ were dried by using a commercially available solvent purification system. $Et_3N$ was dried over KOH followed by distillation from $CaH_2$ and stored under an atmosphere of argon. All moisture-sensitive reac-

tions were performed in flame-dried septum-sealed glassware under an atmosphere of argon. Reagents were transferred by means of syringe. Solids were introduced under a counter-flow of argon. The concentration of commercially available *n*-BuLi solutions was confirmed by titration against diphenylacetic acid.[43]

Analytical TLC was performed using precoated silica gel foils (4 cm). Visualization was achieved using 254 nm ultraviolet irradiation followed by staining with the Kägi–Miescher reagent (*p*-anisaldehyde 2.53% v/v, AcOH 0.96% v/v, EtOH 93.06% v/v, concd $H_2SO_4$ 3.45% v/v) or the $KMnO_4$ reagent [$KMnO_4$ (3 g), $K_2CO_3$ (20 g), NaOH (0.25 g in 5 mL $H_2O$), $H_2O$ (300 mL)].[44] Unless otherwise specified, chromatographic purification[45] was performed on silica gel (particle size 0.040–0.063 mm. Mixtures of cyclohexane and EtOAc or *n*-pentane and $Et_2O$ were used as eluents.

$^1$H NMR spectra were recorded at 400 or 500 MHz. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ (7.26 ppm).[46] Standard abbreviations were used to denote signal splitting patterns. Coupling constants (Hz) are given as reported by the NMR processing and analysis software. $^{13}$C NMR spectra were recorded at 101 or 126 MHz. Unless otherwise reported, all $^{13}$C NMR spectra were obtained with broadband proton decoupling. Chemical shifts are reported in ppm relative to $CDCl_3$ (77.16 ppm); the total number of reported $^{13}$C atom signals may fall short of the expected number because of coincidental chemical shifts, even for constitutopic or diastereotopic carbon atoms. The NMR peak assignment as well as the assignment of the relative configuration rests on the interpretation of $^1$H$^1$H COSY, $^1$H$^{13}$C HSQC, and $^1$H$^1$H NOESY experiments. Atom numbering is based on the curvicollide numbering system (Figure 1) or as stated in the experimental procedure.

Unless stated otherwise, IR spectra were recorded as a thin film on a KBr disk. IR absorptions are reported in reciprocal wavelength ($cm^{-1}$) and are adjusted downward or upward to 0 or 5 $cm^{-1}$. Relative intensities are indicated as they appeared using standard abbreviations. High-resolution mass spectra were recorded on a LTQ Orbitrap mass spectrometer using electrospray ionization (ESI).

Molecular formula assignment was confirmed by combustion elemental analysis using the elemental analyzers Leco CHNS-932 or Elementar Vario Micro Cube. Melting points are uncorrected and were recorded on a Büchi B-540 melting point apparatus.

### Alcohol 8b by Benzyl Ether Cleavage (Scheme 3)

To an ice-cooled solution of the benzyl ether **8a**[11] ($C_{22}H_{34}O_2Si$, 358.60 g/mol, 0.4 g, 1.115 mmol, 1 equiv) in $CH_2Cl_2$ (9 mL) and aq pH 7 buffer (0.9 mL) was added DDQ (227.0 g/mol, 0.46 g, 2.03 mmol, 1.8 equiv). The mixture was stirred at r.t. for 22 h and then diluted by the addition of $H_2O$ (16 mL). The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1 to 20:1) to afford the monoprotected (2*R*,3*S*,4*S*)-3-methyl-2-vinylhex-5-yne-1,4-diol **8b** ($C_{15}H_{28}O_2Si$, 268.47 g/mol, 184 mg, 0.685 mmol, 61%) as light yellow oil; $R_f$ = 0.43 (hexanes–EtOAc, 2:1); $[\alpha]_D^{25}$ +1.5 (*c* 0.9, $CHCl_3$).

IR (film): 3500–3100, 3000–2860, 1470, 1250, 1080, 835 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 3 H), 0.14 (s, 3 H), 0.90 (s, 9 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 1.76–1.82 (m, 1 H), 2.07 (br s, 1 H), 2.40 (d, *J* = 1.9 Hz, 1 H), 2.43–2.49 (m, 1 H), 3.49 (dd, *J* = 10.9, 7.5 Hz, 1 H), 3.73 (dd, *J* = 10.9, 5.6 Hz, 1 H), 4.42 (dd, *J* = 4.6, 1.9 Hz, 1 H), 5.15–5.20 (m, 2 H), 5.68 (ddd, *J* = 17.1, 10.4, 9.1 Hz, 1 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –4.8, –4.2, 11.8, 18.5, 26.1, 41.6, 48.6, 63.1, 66.2, 74.2, 83.5, 118.3, 139.0.

Anal. Calcd for $C_{15}H_{28}O_2Si$: C, 67.11; H, 10.51. Found: C, 67.2; H, 10.2.

### Bis-Silyl Ether 8c (Scheme 3)

To an ice-cooled solution of the alcohol **8b** ($C_{15}H_{28}O_2Si$, 268.47 g/mol, 184 mg, 0.685 mmol, 1 equiv) in $CH_2Cl_2$ (0.7 mL) were successively added imidazole (68.08 g/mol, 70 mg, 1.03 mmol, 1.5 equiv), DMAP (122.17 g/mol, 8 mg, 0.065 mmol, 0.1 equiv), and TBSCl (150.72 g/mol, 113 mg, 0.75 mmol, 1.1 equiv). The mixture was stirred at 0 °C for 1 h and then diluted by the addition of sat. aq $NH_4Cl$ (1 mL). The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 2 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1) to afford the bis-TBS protected (2*R*,3*S*,4*S*)-3-methyl-2-vinylhex-5-yne-1,4-diol **8c** ($C_{21}H_{42}O_2Si_2$, 382.74 g/mol, 240 mg, 0.63 mmol, 92%) as a colorless oil; $R_f$ = 0.66 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ +24.0 (*c* 1.1, $CHCl_3$).

IR (film): 3000–2860, 1470, 1250, 1090, 835 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.01 (s, 3 H), 0.06 (s, 3 H), 0.09 (s, 3 H), 0.86 (s, 9 H), 0.87 (s, 9 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 1.75–1.84 (m, 1 H), 2.08–2.14 (m, 1 H), 2.31 (d, *J* = 2.0 Hz, 1 H), 3.62 (dd, *J* = 9.8, 3.8 Hz, 1 H), 3.67 (dd, *J* = 9.8, 5.3 Hz, 1 H), 4.42 (dd, *J* = 4.6, 2.0 Hz, 1 H), 5.03–5.08 (m, 2 H), 5.74 (ddd, *J* = 17.1, 10.5, 9.3 Hz, 1 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.5, –5.2, –4.7, 11.0, 18.2, 25.7, 40.0, 48.3, 64.0, 65.4, 73.0, 83.3, 116.0, 139.3.

Anal. Calcd for $C_{21}H_{42}O_2Si_2$: C, 65.90; H, 11.06. Found: C, 66.0; H, 11.2.

### Alcohol 9a by Ozonolysis of Enyne 8c (Scheme 3)

Using a commercially available ozonizer, an oxygen–ozone mixture was passed through a solution of the enyne **8c** ($C_{21}H_{42}O_2Si_2$, 382.74 g/mol, 0.8 g, 2.09 mmol, 1 equiv) and Sudan Red B (one crystal) in MeOH (12 mL) and $CH_2Cl_2$ (4 mL) at –78 °C until the raspberry-like color had disappeared. For reductive workup, $PPh_3$ (262.29 g/mol, 1.6 g, 6.1 mmol, 3 equiv) was immediately added and the mixture was stirred at –78 °C for 1 h. For in situ reduction, $NaBH_4$ (37.83 g/mol, 0.24 g, 6.34 mmol, 3 equiv) was added and the mixture was allowed to warm to r.t. overnight. The solvents were evaporated at reduced pressure and the residue was purified by chromatography (hexanes–EtOAc, 50:1 to 20:1 to 10:1) to deliver the bis-TBS protected (2*S*,3*S*,4*S*)-2-(hydroxymethyl)-3-methylhex-5-yne-1,4-diol **9a** ($C_{20}H_{42}O_3Si_2$, 386.72 g/mol, 0.61 g, 1.577 mmol, 75%) as a colorless oil; $R_f$ = 0.5 (hexanes–EtOAc, 5:1); $[\alpha]_D^{25}$ –17.2 (*c* 1.3, $CHCl_3$).

IR (film): 3500–3100, 3000–2860, 1470, 1250, 1080, 835 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.08 (s, 3 H), 0.12 (s, 3 H), 0.87 (s, 9 H), 0.88 (s, 9 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 1.79–1.86 (m, 1 H), 1.91–1.98 (m, 1 H), 2.35 (d, *J* = 2.3 Hz, 1 H), 2.95 (t, *J* = 5.7 Hz, 1 H), 3.71–3.84 (m, 3 H), 3.92 (dd, *J* = 9.9, 3.6 Hz, 1 H), 4.49 (dd, *J* = 4.9, 2.1 Hz, 1 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.8, –5.7, –5.3, –4.7, 11.9, 18.1, 25.7, 37.7, 43.2, 65.2, 65.3, 65.7, 73.2, 83.7.

Anal. Calcd for $C_{20}H_{42}O_3Si$: C, 62.12; H, 10.95. Found: C, 62.3; H, 10.8.

### Tris-Silyl Ether 9b (Scheme 3)

To an ice-cooled solution of the alcohol **9a** ($C_{20}H_{42}O_3Si_2$, 386.72 g/mol, 0.6 g, 1.552 mmol, 1 equiv) in $CH_2Cl_2$ (1.5 mL) were successively added imidazole (68.08 g/mol, 210 mg, 3.085 mmol, 2 equiv), DMAP (122.17 g/mol, 19 mg, 0.156 mmol, 0.1 equiv), and TPSCl (*t*-$BuPh_2SiCl$, 274.86 g/mol, 1.057 g/mL, 0.49 mL, 518 mg, 1.885 mmol, 1.2 equiv).

After stirring at 0 °C for 2 h, the mixture was diluted by the addition of sat. aq $NH_4Cl$ (1 mL). The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 2 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1) to afford the tris-protected (2*R*,3*S*,4*S*)-2-(hydroxymethyl)-3-methylhex-5-yne-1,4-diol **9b** ($C_{36}H_{60}O_3Si_3$, 625.13 g/mol, 0.94 g, 1.504 mmol, 97%) as a colorless oil; $R_f$ = 0.54 (hexanes–EtOAc, 50:1); $[\alpha]_D^{25}$ –9.7 (*c* 1.1, $CHCl_3$).

IR (film): 3000–2860, 1470, 1250, 1080, 837 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = –0.03 (s, 3 H), –0.02 (s, 3 H), 0.03 (s, 3 H), 0.08 (s, 3 H), 0.81 (s, 9 H), 0.85 (s, 9 H), 0.96 (d, *J* = 6.5 Hz, 3 H), 1.02 (s, 9 H), 1.92–1.97 (m, 2 H), 2.31 (d, *J* = 2.0 Hz, 1 H), 3.58 (dd, *J* = 9.8, 6.8 Hz, 1 H), 3.66 (dd, *J* = 9.9, 5.4 Hz, 1 H), 3.76 (dd, *J* = 9.9, 5.1 Hz, 1 H), 3.83 (dd, *J* = 10.0, 3.8 Hz, 1 H), 4.40 (m, 1 H), 7.32–7.38 (m, 6 H), 7.62–7.65 (m, 4 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.3, –4.6, 11.4, 18.0, 18.1, 19.2, 25.7, 25.8, 26.8, 38.4, 44.0, 60.4, 62.8, 65.8, 73.1, 84.3, 127.5, 129.3, 133.8, 133.9, 135.4, 135.5.

Anal. Calcd for $C_{36}H_{60}O_3Si_3$: C, 69.17; H, 9.67. Found: C, 69.2; H, 9.5.

### Ynoate 10a by Nucleophilic Isopropoxycarbonylation (Scheme 3)

To a solution of LDA, prepared from *i*-$Pr_2NH$ (101.19 g/mol, 0.722 g/mL, 0.2 mL, 144.4 mg, 1.427 mmol, 1.3 equiv) and *n*-BuLi (2.2 M in *n*-hexane, 0.7 mL, 1.54 mmol, 1.4 equiv) in THF (2 mL) at –78 °C was added a cooled (–78 °C) solution of the alkyne **9b** ($C_{36}H_{60}O_3Si_3$, 625.13 g/mol, 0.7 g, 1.12 mmol, 1 equiv) in THF (4 mL). The mixture was stirred for 30 min at –78 °C and isopropyl chloroformate (1 M in toluene, 1.5 mL, 1.3 mmol, 1.3 equiv) was slowly added. After stirring at –78 °C for 30 min and at 0 °C for 2 h, the reaction mixture was diluted by the addition of sat. aq $NH_4Cl$ (4 mL). The biphasic mixture was partitioned in a separatory funnel and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1) to yield the tris-protected isopropyl (4*S*,5*S*,6*R*)-4,7-dihydroxy-6-(hydroxymethyl)-5-methylhept-2-ynoate **10a** ($C_{40}H_{66}O_5Si_3$, 711.22 g/mol, 0.68 g, 0.956 mmol, 85%) as a colorless oil; $R_f$ = 0.33 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ –6.1 (*c* 1.1, $CHCl_3$).

IR (film): 3000–2860, 1710, 1470, 1260, 1100, 840 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = –0.03 (s, 3 H), –0.02 (s, 3 H), 0.05 (s, 3 H), 0.11 (s, 3 H), 0.81 (s, 9 H), 0.87 (s, 9 H), 0.97 (d, *J* = 7.0 Hz, 3 H), 1.02 (s, 9 H), 1.25 (d, *J* = 6.3 Hz, 6 H), 1.93–2.05 (m, 2 H), 3.56 (dd, *J* = 10.0, 6.8 Hz, 1 H), 3.62 (dd, *J* = 10.0, 6.0 Hz, 1 H), 3.73–3.81 (m, 2 H), 4.54 (d, *J* = 5.8 Hz, 1 H), 5.05 (sept, *J* = 5.8 Hz, 1 H), 7.33–7.39 (m, 6 H), 7.62–7.65 (m, 4 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.3, –4.6, 11.5, 18.0, 18.1, 19.2, 21.5, 25.6, 25.7, 26.8, 38.7, 43.7, 60.6, 63.0, 65.9, 69.6, 77.7, 87.3, 127.5, 129.4, 133.7, 135.4, 135.5, 153.0.

Anal. Calcd for $C_{40}H_{66}O_5Si_3$: C, 67.55; H, 9.35. Found: C, 67.8; H, 9.2.

### Allylic Alcohol 11a from Ynoate 10a (Scheme 3)

*1,4-Addition*: To an ice-cooled solution of CuBr·$SMe_2$ (205.58 g/mol, 2 g, 9.728 mmol, 10 equiv) in THF (20 mL) was added MeMgBr (1 M in THF, 9.8 mL, 9.8 mmol, 10 equiv). After stirring at 0 °C for 1 h, the solution of the reagent was chilled to –78 °C and a cooled (–78 °C) solution of the ynoate **11a** ($C_{40}H_{66}O_5Si_3$, 711.22 g/mol, 0.7 g, 0.984 mmol, 1 equiv) in THF (20 mL) was added. The reaction mixture was allowed to warm to r.t. overnight and then cooled to 0 °C. Sat. aq $NH_4Cl$ (10 mL) and $H_2O$ (10 mL) were carefully added (gas evolution!). The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1) to afford the enoate and the ynoate **10a** as an inseparable mixture (0.6 g); $R_f$ = 0.57 (hexanes–EtOAc, 20:1).

*DIBAL-H Reduction*: To a solution of the product from the 1,4-addition (86 mg, assumed to be pure $C_{41}H_{70}O_5Si_3$, 727.26 g/mol, 0.1825 mmol, 1 equiv) in $CH_2Cl_2$ (1.2 mL) at –100 °C was slowly added DIBAL-H (1 M in $CH_2Cl_2$, 0.42 mL, 0.42 mmol, 2.3 equiv). After stirring at –100 °C for 1 h, the reaction mixture was diluted by the addition of sat. aq Na/K tartrate (1.2 mL) and stirred at 0 °C for 1 h. The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted times with $CH_2Cl_2$ (3 × 3 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 20:1 to 10:1) to afford the tris-protected (4*S*,5*S*,6*R*,*E*)-6-(hydroxymethyl)-3,5-dimethylhept-2-ene-1,4,7-triol ($C_{38}H_{66}O_4Si_3$, 671.20 g/mol, 54 mg, 0.0805 mmol, 44%) **11a** as a colorless oil, but contaminated with NMR visible but inseparable impurities; $R_f$ = 0.33 (hexanes–EtOAc, 5:1); $[\alpha]_D^{25}$ –5.6 (*c* 1.0, $CHCl_3$).

IR (film): 3000–2860, 1470, 1260, 1100, 840 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = –0.06 (s, 3 H), –0.05 (s, 3 H), 0.04 (s, 3 H), 0.03 (s, 3 H), 0.61 (d, *J* = 7.3 Hz, 3 H), 0.80 (s, 9 H), 0.88 (s, 9 H), 1.02 (s, 9 H), 1.57 (s, 3 H), 2.00–2.07 (m, 1 H), 2.27–2.30 (m, 1 H), 3.43 (dd, *J* = 9.9, 7.9 Hz, 1 H), 3.53 (dd, *J* = 9.8, 8.5 Hz, 1 H), 3.67 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.80 (dd, *J* = 9.8, 5.3 Hz, 1 H), 3.89 (d, *J* = 8.5 Hz, 1 H), 4.15–4.18 (m, 2 H), 5.51 (t, *J* = 6.7 Hz, 1 H), 7.31–7.40 (m, 6 H), 7.62–7.65 (m, 4 H); no OH signal was detected.

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = –5.7, –5.6, –5.2, –4.4, 11.2, 11.6, 18.0, 18.1, 19.2, 25.7, 25.8, 26.7, 34.9, 41.4, 59.1, 60.4, 63.8, 80.8, 125.6, 127.4, 129.3, 133.9, 135.4, 135.5, 140.4.

### Diene 7b by Julia–Kocienski Olefination (Scheme 3)

*$MnO_2$ Oxidation*: To a solution of the allylic alcohol **11a** ($C_{38}H_{66}O_4Si_3$, 671.20 g/mol, 0.17 g, 0.253 mmol, 1 equiv) in $CH_2Cl_2$ (5 mL) was added $MnO_2$ (86.94 g/mol, 0.25 g, 2.76 mmol, 11 equiv) and the mixture was stirred in the dark at 40 °C for 3 h. The mixture was then filtered through Celite and the filter cake was rinsed with $CH_2Cl_2$. The combined filtrates were concentrated in vacuo to afford the corresponding crude enal (0.17 g) as a light yellow oil that was used immediately and without further purification; $R_f$ = 0.66 (hexanes–EtOAc, 5:1).

*Julia–Kocienski Olefination*: To a solution of (*R*)-**12**[11a] ($C_{14}H_{20}N_4O_2S$, 308.40 g/mol, 0.53 g, 1.719 mmol, 7 equiv) in THF (2.5 mL) at –78 °C was added KHMDS (0.5 M in toluene, 3.5 mL, 1.75 mmol, 7 equiv). After stirring at –78 °C for 30 min, a solution of the crude enal (assumed to be pure $C_{38}H_{64}O_4Si_3$, 669.18 g/mol, 0.17 g, 0.254 mmol, 1 equiv) in THF (2.5 mL) was added and the mixture was allowed to warm to r.t. overnight. The reaction mixture was then diluted by the addition of sat. aq $NH_4Cl$ (5 mL). The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1) to afford the tris-silyl protected (2*R*,3*S*,4*S*,5*E*,7*E*,9*R*)-2-(hydroxymethyl)-3,5,9-trimethyltrideca-5,7-diene-1,4-diol **7b** ($C_{45}H_{78}O_3Si_3$, 751.37 g/mol, 0.139 g, 0.185 mmol, 73% from **11a**, *E*/*Z* = 95:5) as a colorless oil, but contaminated with NMR visible impurities that are difficult to separate because of the low polarity of the tris-silyl ether; $R_f$ = 0.57 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ –2.2 (*c* 1.1, $CHCl_3$).

IR (film): 3000–2850, 1470, 1260, 1110, 910 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = –0.06 (s, 3 H), –0.05 (s, 3 H), –0.03 (s, 3 H), 0.03 (s, 3 H), 0.62 (d, *J* = 7.3 Hz, 3 H), 0.81 (s, 9 H), 0.88 (m, 12 H), 0.99 (d, *J* = 6.5 Hz, 3 H), 1.03 (s, 9 H), 1.18–1.27 (m, 6 H), 1.63 (s, 3 H), 2.06–2.12 (m, 1 H), 2.13–2.17 (m, 1 H), 2.29–2.34 (m, 1 H), 3.44 (dd, *J* = 9.8, 8.3 Hz, 1 H), 3.55 (dd, *J* = 9.2, 9.2 Hz, 1 H), 3.70 (dd, *J* = 9.9, 4.9 Hz, 1 H), 3.83 (dd, *J* = 9.8, 5.3 Hz, 1 H), 3.88 (d, *J* = 8.5 Hz, 1 H), 5.47 (dd, *J* = 15.1, 8.0 Hz, 1 H), 5.87 (d, *J* = 10.8 Hz, 1 H), 6.16 (dd, *J* = 15.1, 10.8 Hz, 1 H), 7.32–7.38 (m, 6 H), 7.64–7.66 (m, 4 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.3, –4.6, 11.5, 11.6, 14.0, 18.0, 18.1, 19.2, 20.5, 22.7, 25.7, 25.8, 26.8, 29.5, 35.2, 36.8, 37.0, 41.6, 60.4, 63.8, 81.3, 124.0, 126.9, 127.4, 129.3, 134.0, 134.2, 135.5, 136.6, 140.0.

Anal. Calcd for $C_{45}H_{78}O_3Si_3$: C, 71.93; H, 10.46. Found: C, 72.0; H, 10.1.

### α-Keto Ester (+)-*anti*-4 by Catalytic Asymmetric Gosteli–Claisen Rearrangement in $CH_2Cl_2$–$CF_3CH_2OH$ (1:1) (Scheme 4)

A solution of [Cu{(*S*,*S*)-*tert*-butyl-box}$(H_2O)_2$]$(SbF_6)_2$ [(*S*,*S*)-**3**; $C_{17}H_{34}CuF_{12}N_2O_4Sb_2$, 865.52 g/mol, 0.63 g, 0.728 mmol, 0.05 equiv) in $CF_3CH_2OH$ (15 mL) was stirred for 5 min at r.t. To the turquoise blue solution of (*S*,*S*)- **3** in $CF_3CH_2OH$ was added a solution of (*E*,*Z*)-**2** ($C_{16}H_{20}O_4$, 276.33 g/mol, 4 g, 14.475 mmol, 1 equiv) in $CH_2Cl_2$ (15 mL). The reaction mixture was stirred for about 12 h at r.t. (TLC monitoring). The solvents were subsequently removed at reduced pressure and the residue was purified by chromatography (cyclohexane–EtOAc, 50:1) to provide the α-keto ester **4** ($C_{16}H_{20}O_4$, 276.33 g/mol, 3.8 g, 13.75 mmol, 95%, dr >95:5, 99% ee) as a colorless oil. The ee was determined by HPLC: Chiralpak IA, 4.6 × 250 mm, *n*-heptane–EtOAc, 99:1, 1 mL/min; (3*R*,4*R*)-**4**, $t_R$ = 12.8 min, (3*S*,4*S*)-**4**, $t_R$ = 15.0 min; $R_f$ = 0.6 (cyclohexane–EtOAc, 3:1); $[\alpha]_D^{25}$ +39.7 (*c* 0.89, $CHCl_3$).

IR (film): 1730 (s), 1455 (s), 1260 (s), 1100 (s), 1050 (s) $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.9 Hz, 3 H), 2.83 (qd, *J* = 9.4, 4.9 Hz, 1 H), 3.31–3.39 (m, 2 H), 3.45 (dd, *J* = 9.6, 4.9 Hz, 1 H), 3.62 (s, 3 H), 4.33 (d, *J* = 12.0 Hz, 1 H), 4.37 (d, *J* = 12.0 Hz, 1 H), 5.12–5.13 (m, 2 H), 5.52 (ddd, *J* = 17.6, 9.4, 9.4 Hz, 1 H), 7.22–7.34 (m, 5 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 14.4, 43.1, 48.4, 52.5, 72.4, 72.7, 118.7, 127.6, 128.3, 135.3, 137.5, 161.5, 184.2.

Anal. Calcd for $C_{16}H_{24}O_4$: C, 69.54; H, 7.30. Found: C, 69.3; H, 7.4.

### α-Hydroxy Ester 13a by K-Selectride Reduction (Scheme 4)

Four of the following procedures were run in parallel and were combined for workup. To a solution of the α-keto ester (+)-*anti*-**4** ($C_{16}H_{20}O_4$, 276.33 g/mol, 1 g, 3.619 mmol, 1 equiv) in THF (20 mL) at –100 °C was slowly added K-Selectride (1 M in THF, 4.3 mL, 4.3 mmol, 1.2 equiv). After stirring for 10 min at –100 °C, the reaction mixture was first diluted by the addition of sat. aq $NH_4Cl$ (15 mL) and then warmed to r.t. The four biphasic mixtures were combined in a separatory funnel and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 ×). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 20:1) to afford the α-hydroxy ester **13a** ($C_{16}H_{22}O_4$, 278.35 g/mol, 3.7 g, 13.292 mmol, 92% combined yield, dr >95:5) as a colorless oil; $R_f$ = 0.37 (cyclohexane–EtOAc, 3:1); $[\alpha]_D^{25}$ +14.9 (*c* 0.4, $CHCl_3$).

IR (film): 3600, 3050, 3000, 2850, 1735 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 7.1 Hz, 3 H), 2.12–2.23 (m, 1 H), 2.61–2.70 (m, 1 H), 3.44 (d, *J* = 6.7 Hz, 2 H), 3.74 (s, 3 H), 4.06 (d, *J* = 5.8 Hz, 1 H), 4.46 (d, *J* = 12.1 Hz, 1 H), 4.51 (d, *J* = 12.1 Hz, 1 H), 5.11–5.17 (m, 2 H), 5.73 (ddd, *J* = 17.8, 11.5, 9.4 Hz, 1 H), 7.27–7.36 (m, 5 H); no OH signal was detected.

$^{13}$C NMR (76 MHz, $CDCl_3$): δ = 12.4, 38.0, 44.4, 52.1, 71.5, 72.9, 74.4, 117.8, 127.5, 128.3, 135.6, 136.7, 138.2, 175.1.

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.0; H, 8.1.

### δ-Lactone 14) (Scheme 4)

To a solution of the α-hydroxy ester **13a** ($C_{16}H_{22}O_4$, 278.35 g/mol, 28 mg, 0.1 mmol, 1 equiv) in DMF (1 mL) was added Pd/C (40.4 mg, 10% w/w Pd, 4.04 mg Pd, 106.42 g/mol, 0.038 mmol, 0.38 equiv). The flask was twice evacuated (100 mbar, 1 min) and vented with $H_2$ (balloon). The reaction mixture was then stirred for about 1 h and until TLC indicated complete conversion. The mixture was filtered through Celite and the filter cake was rinsed with $CH_2Cl_2$. The solvents were removed at reduced pressure and the residue was purified by Kugelrohr distillation (70 °C/1 mbar) to afford (3*R*,4*R*,5*R*)-5-ethyl-3-hydroxy-4-methyl-tetrahydropyran-2-one (**14**) ($C_8H_{14}O_3$, 158,20 g/mol, 15.8 mg, 0.10 mmol, dr = 95:5, 99%) as a white solid; mp 91 °C; $R_f$ = 0.54 (hexanes–EtOAc, 1:1); $[\alpha]_D^{25}$ –120.9 (*c* 0.69, $CHCl_3$).

IR (film): 3700–3100, 3080–2870, 1750 $cm^{-1}$.

$^1$H NMR (600 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 7.2 Hz, 3 H), 0.97 (t, *J* = 7.4 Hz, 3 H), 1.43 (m, 2 H), 1.66–1.72 (m, 1 H), 2.21 (m, 1 H), 3.12 (s, 1 H), 3.96 (dd, *J* = 11.6, 11.6 Hz, 1 H), 4.32 (dd, *J* = 11.6, 6.2 Hz, 1 H), 4.45 (d, *J* = 7.7 Hz, 1 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 11.4, 16.5, 25.0, 36.2, 42.3, 67.9, 69.6, 175.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{15}O_3$: 159.1056; found: 159.1014.

### Silyl Ether 13b (Scheme 4)

To an ice-cooled solution of the α-hydroxy ester **13a** ($C_{16}H_{22}O_4$, 278.35 g/mol, 3.4 g, 12.21 mmol, 1 equiv) in $CH_2Cl_2$ (3 mL) and DMF (3 mL) were successively added imidazole (68.08 g/mol, 2.5 g, 36.72 mmol, 3 equiv), DMAP (137.21 g/mol, 0.15 g, 1.09 mmol, 0.1 equiv), and *tert*-butyldimethylsilyl chloride (TBSCl, $C_6H_{15}ClSi$, 150.72 g/mol, 3.7 g, 24.55 mmol, 2 equiv). The cooling bath was removed and the mixture was stirred at r.t. for 3 d. Sat. aq $NH_4Cl$ was added and the resulting biphasic mixture was partitioned in a separatory funnel. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1) to provide the silyl ether **13b** ($C_{22}H_{36}O_4Si$, 392.61 g/mol, 4.6 g, 11.72 mmol, 96%) as a colorless oil; $R_f$ = 0.42 (hexanes–EtOAc, 10:1); $[\alpha]_D^{25}$ +34.0 (*c* 2.68, $CHCl_3$).

IR (film): 3030–2850, 1745 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.02 (s, 3 H), 0.78 (d, *J* = 7.1 Hz, 3 H), 0.89 (s, 9 H), 2.11–2.17 (m, 1 H), 2.69–2.80 (m, 1 H), 3.43 (dd, *J* = 9.4, 6.6 Hz, 1 H), 3.48 (dd, *J* = 9.5, 6.6 Hz, 1 H), 3.65 (s, 3 H), 4.00 (d, *J* = 7.2 Hz, 1 H), 4.43 (d, *J* = 12.1 Hz, 1 H), 4.52 (d, *J* = 12.2 Hz, 1 H), 5.03–5.14 (m, 2 H), 5.70 (ddd, *J* = 17.2, 10.4, 8.9 Hz, 1 H), 7.26–7.31 (m, 5 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.4, –5.1, 11.7, 18.1, 25.6, 37.8, 43.0, 51.4, 71.5, 72.5, 75.2, 117.3, 127.3, 127.4, 128.2, 136.4, 138.4, 173.8.

Anal. Calcd for $C_{22}H_{36}O_4Si$: C, 67.30; H, 9.24. Found: C, 67.5; H, 9.3.

### Alcohol 15 by DIBAL-H Reduction (Scheme 4)

To a solution of the ester **13b** ($C_{22}H_{36}O_4Si$, 392.61 g/mol, 4.6 g, 11.71 mmol, 1 equiv) in $CH_2Cl_2$ (4 mL) at –78 °C was slowly added DIBAL-H (1 M in $CH_2Cl_2$, 35 mL, 35 mmol, 3 equiv). The mixture was stirred at –78 °C for 1 h and then diluted at 0 °C by the careful addition of aq pH 7 buffer (24 mL) and sat. aq Na/K tartrate (48 mL). Stirring was contin-

ued for 1 h at 0 °C. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (cyclohexane–EtOAc, 50:1 to 20:1) yielded the bis-protected (2*R*,3*R*,4*R*)-3-methyl-4-vinylpentane-1,2,5-triol **15** ($C_{21}H_{36}O_3Si$, 364.60 g/mol, 3.5 g, 9.6 mmol, 82%) as a colorless oil; $R_f$ = 0.50 (hexanes–EtOAc, 3:1); $[\alpha]_D^{25}$ +16.5 (*c* 0.51, $CHCl_3$).

IR (film): 3650–3200, 3070–2860 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6 H), 0.75 (d, *J* = 7.2 Hz, 3 H), 0.83 (s, 9 H), 1.93–2.00 (m, 2 H), 2.46–2.55 (m, 1 H), 3.42 (dd, *J* = 9.2, 7.4 Hz, 1 H), 3.47 (dd, *J* = 9.2, 6.2 Hz, 1 H), 3.51–3.61 (m, 1 H), 3.67–3.71 (m, 1 H), 4.39 (d, *J* = 12.0 Hz, 1 H), 4.46 (d, *J* = 12.0 Hz, 1 H), 4.95–5.03 (m, 2 H), 5.63 (ddd, *J* = 17.0, 10.6, 8.7 Hz, 1 H), 7.18–7.29 (m, 5 H); no OH signal detected.

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = –4.5, –4.3, 11.4, 18.1, 25.9, 36.6, 44.1, 63.6, 72.4, 72.9, 75.0, 116.7, 127.5, 127.6, 128.3, 137.5, 138.4.

Anal. Calcd for $C_{21}H_{36}O_3Si$: C, 69.18; H, 9.97. Found: C, 69.2; H, 10.0.

### Aldehyde 5b by Dess–Martin Oxidation (Scheme 4)

To an ice-cooled solution of the alcohol **15** ($C_{21}H_{36}O_3Si$, 364.60 g/mol, 3.5 g, 9.6 mmol, 1 equiv) in $CH_2Cl_2$ (20 mL) and pyridine (10 mL) was added the Dess–Martin periodinane (424.14 g/mol, 6 g, 14.15 mmol, 1.5 equiv). The cooling bath was removed and the mixture was stirred for 2 h at r.t. The reaction mixture was subsequently diluted by the addition of sat. aq $NH_4Cl$ (15 mL). The phases were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (hexanes–EtOAc, 50:1) afforded the bis-protected (2*R*,3*R*,4*R*)-2-hydroxy-4-(hydroxymethyl)-3-methylhex-5-enal **5b** ($C_{21}H_{34}O_3Si$, 362.59 g/mol, 3.3 g, 9.1 mmol, 95%) as a colorless oil; $R_f$ = 0.78 (hexanes–EtOAc, 3:1); $[\alpha]_D^{25}$ +37.6 (*c* 0.36, $CHCl_3$).

IR (film): 3070–2850, 1735 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = –0.01 (s, 3 H), 0.00 (s, 3 H), 0.83 (d, *J* = 7.2 Hz, 3 H), 0.88 (s, 9 H), 2.15 (m, 1 H), 2.59 (dddd, *J* = 9.0, 5.9, 5.9, 5.9 Hz, 1 H), 3.37 (dd, *J* = 9.5, 6.5 Hz, 1 H), 3.44 (dd, *J* = 9.5, 5.9 Hz, 1 H), 3.80 (dd, *J* = 6.0, 2.4 Hz, 1 H), 4.36 (d, *J* = 12.0 Hz, 1 H), 4.45 (d, *J* = 12.0 Hz, 1 H), 4.99–5.08 (m, 2 H), 5.68 (ddd, *J* = 17.1, 10.5, 8.9 Hz, 1 H), 7.24–7.37 (m, 5 H), 9.48 (d, *J* = 2.4 Hz, 1 H).

$^{13}C$ NMR (76 MHz, $CDCl_3$): δ = –5.0, –4.4, 12.7, 18.2, 25.7, 36.1, 43.7, 71.6, 72.7, 80.4, 117.2, 127.5, 127.6, 128.3, 137.1, 138.4, 203.7.

Anal. Calcd for $C_{21}H_{34}O_3Si$: C, 69.56; H, 9.45. Found: C, 69.5; H, 9.4.

### Alkyne 8d by Two-Step Homologation (Scheme 4)

*Chloromethylenation*: To an ice-cooled suspension of $ClCH_2PPh_3Cl$ (347.22 g/mol, 8.7 g, 25.06 mmol, 2.8 equiv) in THF (50 mL) was slowly added *n*-BuLi (2.3 M in *n*-hexane, 8.3 mL, 19.09 mmol, 2.1 equiv). The cooling bath was removed and the stirring was continued for 2 h. The mixture was cooled to 0 °C and a solution of the aldehyde **5b** ($C_{21}H_{34}O_3Si$, 362.59 g/mol, 3.3 g, 9.1 mmol, 1 equiv) in THF (25 mL) was added. After stirring for 5 min at 0 °C, the reaction mixture was diluted by the addition pentane (300 mL) and filtered through a plug of silica gel. The filter cake was thoroughly washed with pentane and the combined filtrates were concentrated at reduced pressure. The crude vinyl chloride was used without further purification.

*β-Elimination*: To a solution of LDA, prepared from *i*-$Pr_2NH$ (101.19 g/mol, 0.722 g/mL, 3.4 mL, 2.455 g, 24.26 mmol, 2.7 equiv) and *n*-BuLi (2.3 M in *n*-hexane, 10.3 mL, 23.69 mmol, 2.5 equiv), in THF (36 mL) at –78 °C was added a cooled (–78 °C) solution of the crude vinyl chloride (assumed 9.1 mmol, 1 equiv) in THF (45 mL). After stirring at –78 °C for 5 min, the mixture was diluted by the addition of sat. aq $NH_4Cl$ (50 mL). The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1) to afford the bis-protected (2*R*,3*R*,4*R*)-3-methyl-2-vinylhex-5-yne-1,4-diol **8d** ($C_{22}H_{34}O_2Si$, 358.60 g/mol, 2.9 g, 8.09 mmol, 89%) as a colorless oil; $R_f$ = 0.65 (hexanes–EtOAc, 10:1); $[\alpha]_D^{25}$ +12.5 (c 1.34, $CHCl_3$).

IR (film): 3070–2860, 1080 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3 H), 0.12 (s, 3 H), 0.88 (s, 9 H), 0.90 (d, *J* = 7.0 Hz, 3 H), 1.90–1.93 (m, 1 H), 2.36 (d, *J* = 2.0 Hz, 1 H), 2.68–2.74 (m, 1 H), 3.47–3.52 (m, 2 H), 4.27 (dd, *J* = 7.2, 2.1 Hz, 1 H), 4.45 (d, *J* = 12.1 Hz, 1 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 5.05–5.10 (m, 2 H), 5.70 (ddd, *J* = 17.0, 10.4, 9.2 Hz, 1 H), 7.25–7.31 (m, 5 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = –5.1, –4.4, 11.3, 18.1, 25.8, 40.1, 43.8, 65.2, 71.8, 72.6, 73.4, 84.4, 117.1, 127.4, 128.2, 136.9, 138.4.

Anal. Calcd for $C_{22}H_{34}O_2Si$: C, 73.69; H, 9.56. Found: C, 73.9; H, 9.3.

### Alcohol 8e by Benzyl Ether Cleavage (Scheme 4)

To an ice-cooled solution of the benzyl ether **8d** ($C_{22}H_{34}O_2Si$, 358.60 g/mol, 0.4 g, 1.115 mmol, 1 equiv) in $CH_2Cl_2$ (9 mL) and aq pH 7 buffer (0.8 mL) was added DDQ (227.00 g/mol, 0.3 g, 1.32 mmol, 1.2 equiv). After stirring 15 h at r.t., additional DDQ (0.2 g, 0.88 mmol, 0.8 equiv) was added and stirring was continued for 24 h. The mixture was diluted by the addition of $H_2O$ (16 mL) and the resulting biphasic mixture was partitioned in a separatory funnel. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1 to 20:1) to provide the monoprotected (2*R*,3*R*,4*R*)-3-methyl-2-vinylhex-5-yne-1,4-diol **8e** ($C_{15}H_{28}O_2Si$, 268.47 g/mol, 200 mg, 0.745 mmol, 67%) as a colorless oil; $R_f$ = 0.57 (hexanes–EtOAc, 2:1); $[\alpha]_D^{25}$ +35.9 (*c* 1.0, $CHCl_3$).

IR (film): 3500–3100, 3000–2860, 1470, 1250, 1080, 835 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 3 H), 0.13 (s, 3 H), 0.88 (s, 9 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 1.40–1.43 (m, 1 H), 1.77–1.86 (m, 1 H), 2.38 (d, *J* = 2.3 Hz, 1 H), 2.50–2.57 (m, 1 H), 3.55 (ddd, *J* = 10.7, 8.2, 4.1 Hz, 1 H), 3.62 (ddd, *J* = 10.6, 8.2, 5.5 Hz, 1 H), 4.24 (dd, *J* = 6.7, 2.3 Hz, 1 H), 5.11–5.21 (m, 2 H), 5.65 (ddd, *J* = 17.2, 10.2, 9.4 Hz, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = –5.2, –4.5, 12.0, 18.0, 25.7, 40.7, 47.4, 63.9, 65.2, 73.6, 84.1, 118.6, 136.7.

Anal. Calcd for $C_{15}H_{28}O_2Si$: C, 67.11; H, 10.51. Found: C, 67.2; H, 10.4.

### PMB Ether 8f from Alcohol 8e (Scheme 4)

To a solution of the alcohol **8e** ($C_{15}H_{28}O_2Si$, 268.47 g/mol, 0.46 g, 1.71 mmol, 1 equiv) in toluene (17 mL) at r.t. was added 2-[(4-methoxybenzyl)oxy]-3-nitropyridine (PMBONPy, $C_{13}H_{12}N_2O_4$, 260.25 g/mol, 0.67 g, 2.57 mmol, 1.5 equiv) and $Cu(OTf)_2$ (361.67 g/mol, 62 mg, 0.171 mmol, 0.1 equiv). After stirring for 18 h at r.t., the mixture was diluted by the addition of sat. aq $NH_4Cl$ (10 mL). The biphasic mixture was partitioned in a separatory funnel. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated at reduced pressure. The residue was purified by chromatography (hexanes–EtOAc, 100:1) to yield the bis-protected (2*R*,3*R*,4*R*)-3-methyl-2-vinylhex-5-yne-1,4-diol **8f** ($C_{23}H_{36}O_3Si$, 388.62 g/mol, 0.58 g, 1.493 mmol, 87%); $R_f$ = 0.5 (hexanes–EtOAc, 10:1); $[\alpha]_D^{25}$ +36.5 (*c* 1.05, $CHCl_3$).

IR (film): 3070–2860, 1610, 1515, 1250, 1080, 835 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3 H), 0.11 (s, 3 H), 0.87–0.89 (m, 12 H), 1.90–1.95 (m, 1 H), 2.35 (d, *J* = 2.3 Hz, 1 H), 2.65–2.72 (m, 1 H), 3.41 (dd, *J* = 9.7, 6.4 Hz, 1 H), 3.45 (dd, *J* = 9.4, 6.4 Hz, 1 H), 3.78 (s, 3 H), 4.26 (dd, *J* = 7.2, 2.3 Hz, 1 H), 4.38 (d, *J* = 11.5 Hz, 1 H), 4.44 (d, *J* = 11.5 Hz, 1 H), 5.03–5.09 (m, 2 H), 5.68 (ddd, *J* = 17.1, 10.3, 8.9 Hz, 1 H), 6.80 (d, *J* = 8.5 Hz, 2 H), 7.25–7.21 (m, 2 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.1, –4.4, 11.3, 18.1, 25.8, 40.0, 43.8, 55.1, 65.2, 71.5, 72.2, 73.4, 84.4, 113.6, 117.0, 129.0, 130.5, 136.9, 158.9.

Anal. Calcd for $C_{22}H_{34}O_2Si$: C, 71.08; H, 9.34. Found: C, 71.5; H, 9.0.

### Alcohol 9c by Ozonolysis of Enyne 8d (Scheme 4)

Using a commercially available ozonizer, an ozone–oxygen mixture was passed through a solution of the enyne **8d** ($C_{22}H_{34}O_2Si$, 358.60 g/mol, 2.9 g, 8.09 mmol, 1 equiv) and Sudan Red B (one crystal) in MeOH (48 mL) and $CH_2Cl_2$ (16 mL) at –78 °C until the raspberry-like color had disappeared. $PPh_3$ (262.29 g/mol, 6.3 g, 24.02 mmol, 3 equiv) was immediately added and the mixture was stirred at –78 °C for 2 h. $NaBH_4$ (37.83 g/mol, 0.91 g, 24.06 mmol, 3 equiv) was added and the mixture was allowed to warm to r.t. overnight. The solvents were evaporated at reduced pressure and the residue was purified by chromatography (hexanes–EtOAc, 50:1 to 20:1) to deliver the bis-protected (3*R*,4*R*)-2-(hydroxymethyl)-3-methylhex-5-yne-1,4-diol **9c** ($C_{21}H_{34}O_3Si$, 362.59 g/mol, 2.3 g, 6.34 mmol, 78%) as a colorless oil; $R_f$ = 0.37 (hexanes–EtOAc, 5:1); $[\alpha]_D^{25}$ +12.9 (*c* 1.18, $CHCl_3$).

IR (film): 3600–3350, 3300, 3000–2800, 1380, 1080 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 3 H), 0.14 (s, 3 H), 0.89 (s, 9 H), 0.98 (d, *J* = 7.0 Hz, 3 H), 1.97–2.04 (m, 1 H), 2.21–2.28 (m, 1 H), 2.41 (d, *J* = 2.0 Hz, 1 H), 3.11 (dd, *J* = 7.4, 4.1 Hz, 1 H), 3.51 (dd, *J* = 9.4, 5.4 Hz, 1 H), 3.57 (dd, *J* = 9.5, 6.5 Hz, 1 H), 3.60–3.66 (m, 1 H), 3.68–3.74 (m, 1 H), 4.40 (dd, *J* = 4.5, 2.0 Hz, 1 H), 4.48 (d, *J* = 12.1 Hz, 1 H), 4.51 (d, *J* = 12.1 Hz, 1 H), 7.28–7.32 (m, 5 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.3, –4.8, 11.8, 18.1, 25.6, 38.4, 41.3, 62.4, 66.0, 72.0, 73.1, 73.8, 83.5, 127.5, 127.6, 128.3, 137.9.

Anal. Calcd for $C_{21}H_{34}O_3Si$: C, 69.56; H, 9.45. Found: C, 69.2; H, 9.2.

### Alcohol 9d by Ozonolysis of Enyne 8f (Scheme 4)

Following the procedure reported for enyne **8d**, the ozonolysis of **8f** ($C_{23}H_{36}O_3Si$, 388.62 g/mol, 0.7 g, 1.8 mmol, 1 equiv) in MeOH (48 mL) and $CH_2Cl_2$ (16 mL) with subsequent addition of $PPh_3$ (262.29 g/mol, 1.4 g, 5.34 mmol, 3 equiv) and $NaBH_4$ (37.83 g/mol, 0.21 g, 5.55 mmol, 3 equiv) delivered **9d** ($C_{22}H_{36}O_4Si$, 392.61 g/mol, 0.54 g, 1.375 mmol, 76%) as a colorless oil; $R_f$ = 0.33 (hexanes–EtOAc, 5:1). Characterization of **9d** rests on $^1$H NMR data only.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 3 H), 0.13 (s, 3 H), 0.89 (s, 9 H), 0.97 (d, *J* = 7.0 Hz, 3 H), 1.95–2.03 (m, 1 H), 2.18–2.25 (m, 1 H), 2.40 (d, *J* = 2.3 Hz, 1 H), 3.12 (dd, *J* = 7.4, 4.4 Hz, 1 H), 3.48 (dd, *J* = 9.3, 5.3 Hz, 1 H), 3.53 (dd, *J* = 9.5, 6.5 Hz, 1 H), 3.59–3.64 (m, 1 H), 3.67–3.72 (m, 1 H), 3.78 (s, 3 H), 4.39 (dd, *J* = 4.6, 1.9 Hz, 1 H), 4.40 (d, *J* = 11.3 Hz, 1 H), 4.44 (d, *J* = 12.1 Hz, 1 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 7.23 (d, *J* = 8.5 Hz, 2 H).

### Silyl Ether 9e from Alcohol 9c (Scheme 5)

To an ice-cooled solution of the alcohol **9c** ($C_{21}H_{34}O_3Si$, 362.59 g/mol, 1.2 g, 3.31 mmol, 1 equiv) in $CH_2Cl_2$ (3 mL) were successively added imidazole (68.08 g/mol, 0.66 g, 9.69 mmol, 3 equiv), DMAP (137.21 g/mol, 40 mg, 0.292 mmol, 0.1 equiv), and TBSCl ($C_6H_{15}ClSi$, 150.72 g/mol, 0.74 g, 4.91 mmol, 1.5 equiv). The cooling bath was removed and the mixture was stirred at r.t. for 2 h. Sat. aq $NH_4Cl$ (2 mL) was added and the resulting biphasic mixture was partitioned in a separatory funnel. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 50:1) to provide the tris-protected (2*R*,3*R*,4*R*)-2-(hydroxymethyl)-3-methylhex-5-yne-1,4-diol **9e** ($C_{27}H_{48}O_3Si_2$, 476.85 g/mol, 1.5 g, 3.146 mmol, 95%) as a colorless oil; $R_f$ = 0.37 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ +14.3 (*c* 1.23, $CHCl_3$).

IR (film): 3000–2800, 1085, 835 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6 H), 0.07 (s, 3 H), 0.11 (s, 3 H), 0.86 (s, 9 H), 0.88 (s, 9 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 1.88–1.94 (m, 1 H), 1.95–2.00 (m, 1 H), 2.35 (d, *J* = 2.3 Hz, 1 H), 3.55–3.61 (m, 3 H), 3.79 (dd, *J* = 9.9, 4.1 Hz, 1 H), 4.43–4.51 (m, 3 H), 7.24–7.32 (m, 5 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.3, –4.7, 11.6, 18.0, 18.1, 25.7, 25.8, 38.6, 41.9, 60.9, 65.5, 69.1, 72.8, 73.0, 84.2, 127.3, 127.4, 128.2, 138.6.

Anal. Calcd for $C_{27}H_{48}O_3Si_2$: C, 68.01; H, 10.15. Found: C, 67.8; H, 9.9.

### Silyl Ether 9f from Alcohol 9d (Scheme 5)

Following the procedure for the preparation of **9e** from **9c**, **9d** ($C_{22}H_{36}O_4Si$, 392.61 g/mol, 0.5 g, 1.274 mmol, 1 equiv) in $CH_2Cl_2$ (1.4 mL) was reacted with imidazole (68.08 g/mol, 0.28 g, 4.11 mmol, 3 equiv), DMAP (137.21 g/mol, 17 mg, 0.124 mmol, 0.1 equiv), and TBSCl ($C_6H_{15}ClSi$, 150.72 g/mol, 0.31 g, 2.06 mmol, 1.5 equiv) to yield **9f** ($C_{28}H_{50}O_4Si_2$, 506.87 g/mol, 0.63 g, 1.243 mmol, 97%) as a colorless oil; $R_f$ = 0.46 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ +13.1 (*c* 1.13, $CHCl_3$).

IR (film): 3000–2800, 1515, 1250, 1085, 835 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6 H), 0.05 (s, 3 H), 0.09 (s, 3 H), 0.85 (s, 9 H), 0.87 (s, 9 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 1.88–1.92 (m, 1 H), 1.92–2.00 (m, 1 H), 2.33 (d, *J* = 2.0 Hz, 1 H), 3.50–3.52 (m, 2 H), 3.54–3.58 (m, 1 H), 3.74–3.76 (m, 1 H), 3.78 (s, 3 H), 4.36 (d, *J* = 11.5 Hz, 1 H), 4.41 (d, *J* = 11.5 Hz, 1 H), 4.46 (dd, *J* = 5.3 Hz, 2.3 Hz, 1 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 7.23 (d, *J* = 7.8 Hz, 2 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.3, –4.7, 11.6, 18.0, 18.1, 25.7, 25.8, 38.6, 41.8, 55.2, 60.9, 65.5, 68.8, 72.4, 73.0, 84.2, 113.5, 129.1, 130.8, 158.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{50}O_4Si_2Na$: 529.3140; found: 529.3144.

### Ynoate 10b from Alkyne 9e (Scheme 5)

To a solution of LDA, prepared from *i*-$Pr_2NH$ (101.19 g/mol, 0.722 g/mL, 0.12 mL, 86.6 mg, 0.856 mmol, 1.2 equiv) and *n*-BuLi (2.3 M in *n*-hexane, 0.37 mL, 0.851 mmol, 1.2 equiv) in THF (1.5 mL) at –78 °C was added a cooled (–78 °C) solution of the alkyne **9e** ($C_{27}H_{48}O_3Si_2$, 476.85 g/mol, 0.34 g, 0.713 mmol, 1 equiv) in THF (3 mL). The mixture was stirred for 15 min at –78 °C and isopropyl chloroformate (1 M in toluene, 0.9 mL, 0.92 mmol, 1.3 equiv) was slowly added. After stirring at –78 °C for 30 min and at 0 °C for 15 min, the reaction mixture was diluted by the addition of sat. aq $NH_4Cl$ (4 mL). The biphasic mixture was partitioned in a separatory funnel and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1) to yield the tris-protected isopropyl (4*R*,5*R*,6*R*)-4,7-dihydroxy-6-(hydroxymethyl)-5-methylhept-2-ynoate **10b** ($C_{31}H_{54}O_5Si_2$, 562.94 g/mol, 0.35 g, 0.622 mmol, 87%) as a colorless oil; $R_f$ = 0.56 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ +5.5 (*c* 0.69, $CHCl_3$).

IR (film): 3000–2850, 1710, 1630, 1250, 1100, 835 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6 H), 0.06 (s, 3 H), 0.11 (s, 3 H), 0.85 (s, 9 H), 0.87 (s, 9 H), 1.00 (d, *J* = 6.5 Hz, 3 H), 1.24 (d, *J* = 6.3 Hz, 6 H), 1.94–1.97 (m, 2 H), 3.54 (d, *J* = 4.8 Hz, 2 H), 3.57–3.61 (m, 1 H), 3.76 (dd, *J* = 9.9, 3.9 Hz, 1 H), 4.43 (d, *J* = 12.1 Hz, 1 H), 4.48 (d, *J* = 11.8 Hz, 1 H), 4.59 (d, *J* = 5.3 Hz, 1 H), 5.05 (sept, *J* = 6.3 Hz, 1 H), 7.23–7.31 (m, 5 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.3, –4.7, 11.8, 18.0, 21.5, 25.6, 25.8, 38.8, 41.6, 60.9, 65.6, 69.1, 69.6, 72.8, 77.5, 87.2, 127.3, 127.5, 128.2, 138.5, 153.0.

Anal. Calcd for $C_{31}H_{54}O_5Si_2$: C, 66.14; H, 9.67. Found: C, 66.3; H, 9.5.

### Ynoate 10c from Alkyne 9f (Scheme 5)

Following the procedure for the synthesis of **10b** from **9e**, a solution of LDA, prepared from *i*-$Pr_2NH$ (101.19 g/mol, 0.722 g/mL, 0.26 mL, 187.7 mg, 1.855 mmol, 2 equiv) and *n*-BuLi (2.1 M in *n*-hexane, 0.9 mL, 1.89 mmol, 2 equiv) in THF (4 mL) was reacted with **9f** ($C_{28}H_{50}O_4Si_2$, 506.87 g/mol, 0.46 g, 0.908 mmol, 1 equiv) in THF (4 mL) and isopropyl chloroformate (1 M in toluene, 1.8 mL, 1.8 mmol, 2 equiv) to afford **10c** ($C_{32}H_{56}O_6Si_2$, 592.96 g/mol, 0.42 g, 0.708 mmol, 78%) as a colorless oil; $R_f$ = 0.33 (hexanes–EtOAc, 10:1).

IR (film): 3000–2850, 1710, 1250, 1090, 835 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.01 (s, 3 H), 0.05 (s, 3 H), 0.10 (s, 3 H), 0.85 (s, 9 H), 0.87 (s, 9 H), 1.00 (d, *J* = 6.5 Hz, 3 H), 1.25 (d, *J* = 6.3 Hz, 6 H), 1.92–1.97 (m, 2 H), 3.49–3.50 (m, 2 H), 3.56 (dd, *J* = 10.0, 6.5 Hz, 1 H), 3.74 (dd, *J* = 10.0, 3.8 Hz, 1 H), 3.78 (s, 3 H), 4.36 (d, *J* = 11.8 Hz, 1 H), 4.41 (d, *J* = 11.3 Hz, 1 H), 4.58 (d, *J* = 5.3 Hz, 1 H), 5.04 (sept, *J* = 6.3 Hz, 1 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 7.22 (d, *J* = 9.5 Hz, 2 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.3, –4.7, 11.8, 18.0, 18.1, 21.5, 25.6, 25.8, 38.8, 41.5, 55.1, 61.0, 65.6, 68.8, 69.6, 72.5, 77.5, 87.2, 113.6, 129.0, 130.6, 153.0, 158.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{57}O_6Si_2$: 593.3688; found: 593.3689.

### Enoate 16a by 1,4-Addition (Scheme 5)

To an ice-cooled solution of CuBr·$SMe_2$ (205.58 g/mol, 3.1 g, 15.08 mmol, 10 equiv) in THF (68 mL) was added MeMgBr (1 M in THF, 15.3 mL, 15.3 mmol, 10 equiv). After stirring at 0 °C for 1 h, the solution of the reagent was chilled to –78 °C and a cooled (–78 °C) solution of the ynoate **10b** ($C_{31}H_{54}O_5Si_2$, 562.94 g/mol, 0.86 g, 1.528 mmol, 1 equiv) in THF (45 mL) was added. The reaction mixture was allowed to warm to r.t. overnight and then cooled to 0 °C. Sat. aq $NH_4Cl$ (20 mL) and $H_2O$ (20 mL) were carefully added (gas evolution!). The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1) to afford the tris-protected isopropyl (4*R*,5*R*,6*R*,*E*)-4,7-dihydroxy-6-(hydroxymethyl)-3,5-dimethylhept-2-enoate **16a** ($C_{32}H_{58}O_5Si_2$, 578.98 g/mol, 0.88 g, 1.52 mmol, 99%, *E*/*Z* >95:5) as a colorless oil; $R_f$ = 0.51 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ +14.2 (*c* 1.02, $CHCl_3$).

IR (film): 3000–2850, 1710, 1250, 1090, 835 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = –0.04 (s, 3 H), –0.01 (s, 3 H), 0.00 (s, 3 H), 0.04 (s, 3 H), 0.72 (d, *J* = 7.3 Hz, 3 H), 0.84 (s, 9 H), 0.88 (s, 9 H), 1.22 (d, *J* = 6.3 Hz, 6 H), 1.98–2.01 (m, 1 H), 2.04 (s, 3 H), 2.21–2.24 (m, 1 H), 3.43 (dd, *J* = 9.5, 8.4 Hz, 1 H), 3.48 (dd, *J* = 9.8, 7.8 Hz, 1 H), 3.57 (dd, *J* = 9.5, 5.3 Hz, 1 H), 3.70 (m, 1 H), 3.94 (d, *J* = 7.5 Hz, 1 H), 4.40 (d, *J* = 12.0 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 5.00 (sept, *J* = 6.3 Hz, 1 H), 5.76 (s, 1 H), 7.23–7.30 (m, 5 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.2, –4.6, 12.2, 14.2, 18.0, 18.1, 21.9, 25.7, 25.8, 35.8, 38.9, 60.6, 66.7, 70.3, 72.5, 81.1, 117.3, 127.2, 127.4, 128.1, 138.7, 159.3, 166.1.

Anal. Calcd for $C_{32}H_{58}O_5Si_2$: C, 66.38; H, 10.10. Found: C, 66.5; H, 10.1.

### Enoate 16b by 1,4-Addition (Scheme 5)

According to the procedure for the preparation of **16a** from **10b**, **10c** ($C_{32}H_{56}O_6Si_2$, 592.96 g/mol, 0.42 g, 0.708 mmol, 1 equiv) in THF (14 mL) was treated with the reagent prepared from CuBr·$SMe_2$ (205.58 g/mol, 1.5 g, 7.296 mmol, 10 equiv) in THF (14 mL) and MeMgBr (1 M in THF, 7.0 mL, 7 mmol, 10 equiv) to afford **16b** ($C_{33}H_{60}O_6Si_2$, 609.01 g/mol, 0.3 g, 0.493 mmol, 70%, *E*/*Z* = 95:5) as a colorless oil; $R_f$ = 0.56 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ not determined.

IR (film): 3000–2850, 1715, 1110, 835 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = –0.05 (s, 3 H), –0.01 (s, 3 H), 0.00 (s, 3 H), 0.03 (s, 3 H), 0.71 (d, *J* = 7.3 Hz, 3 H), 0.84 (s, 9 H), 0.87 (s, 9 H), 1.22 (d, *J* = 6.0 Hz, 6 H), 1.95–2.00 (m, 1 H), 2.03 (s, 3 H), 2.19–2.25 (m, 1 H), 3.39 (dd, *J* = 9.5, 8.0 Hz, 1 H), 3.47 (dd, *J* = 9.9, 7.7 Hz, 1 H), 3.53 (dd, *J* = 9.7, 5.4 Hz, 1 H), 3.71 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.77 (s, 3 H), 3.95 (m, 1 H), 4.32 (d, *J* = 11.5 Hz, 1 H), 4.43 (d, *J* = 11.5 Hz, 1 H), 5.00 (sept, *J* = 6.3 Hz, 1 H), 5.75 (s, 1 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 7.22 (d, *J* = 8.8 Hz, 2 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.2, –4.6, 12.1, 14.2, 18.0, 18.1, 21.8, 25.7, 25.8, 35.7, 38.8, 55.1, 60.6, 66.6, 69.9, 72.0, 81.0, 113.5, 117.3, 128.9, 130.1, 158.9, 159.3, 166.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{61}O_6Si_2$: 609.4001; found: 609.4002.

### Allylic Alcohol 11b by DIBAL-H Reduction (Scheme 5)

To a solution of the enoate **16a** ($C_{32}H_{58}O_5Si_2$, 578.98 g/mol, 0.49 g, 0.846 mmol, 1 equiv) in $CH_2Cl_2$ (8 mL) at –100 °C was slowly added a solution of DIBAL-H in $CH_2Cl_2$ (1 M, 2.5 mL, 2.5 mmol, 3 equiv). After stirring at –100 °C for 1 h, the mixture was diluted by the addition of aq pH 7 buffer (3 mL) and sat. aq Na/K tartrate (8 mL) and stirring was continued for 1 h at 0 °C. The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 20:1 to 10:1) to afford the tris-protected (4*R*,5*R*,6*R*,*E*)-6-(hydroxymethyl)-3,5-dimethylhept-2-ene-1,4,7-triol **11b** ($C_{29}H_{54}O_4Si_2$, 522.92 g/mol, 0.45 g, 0.861 mmol, 99%) as a colorless oil; $R_f$ = 0.40 (cyclohexane–EtOAc, 5:1); $[\alpha]_D^{22}$ +12.9 (c 0.99, $CHCl_3$).

IR (film): 3400–3000, 3000–2850, 1470, 1255, 835 $cm^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = –0.04 (s, 3 H), 0.00 (s, 3 H), 0.01 (s, 3 H), 0.04 (s, 3 H), 0.68 (d, *J* = 7.3 Hz, 3 H), 0.86 (s, 9 H), 0.87 (s, 9 H), 1.57 (s, 3 H), 1.88–1.92 (m, 1 H), 2.29–2.32 (m, 1 H), 3.45 (dd, *J* = 9.5, 8.0 Hz, 1 H), 3.50 (dd, *J* = 9.8, 7.5 Hz, 1 H), 3.58 (dd, *J* = 9.5, 5.5 Hz, 1 H), 3.71 (dd, *J* = 9.8, 4.9 Hz, 1 H), 3.89 (d, *J* = 8.5 Hz, 1 H), 4.16–4.17 (m, 2 H), 4.41 (d, *J* = 11.8 Hz, 1 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 5.52 (t, *J* = 6.4 Hz, 1 H), 7.24–7.31 (m, 5 H); no OH signal detected.

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.2, –4.4, 11.3, 12.0, 18.0, 18.1, 25.8, 35.6, 38.8, 59.1, 60.6, 70.6, 72.4, 81.0, 125.8, 127.2, 127.4, 128.2, 138.8, 140.2.

Anal. Calcd for $C_{29}H_{54}O_4Si_2$: C, 66.61; H, 10.41. Found: C, 66.9; H, 10.2.

### Allylic Alcohol 11c by DIBAL-H Reduction (Scheme 5)

Following the procedure for the preparation of **11b** from **16a**, **16b** ($C_{33}H_{60}O_6Si_2$, 609.01 g/mol, 0.3 g, 0.493 mmol, 1 equiv) in $CH_2Cl_2$ (5 mL) was treated with DIBAL-H (1 M in $CH_2Cl_2$, 1.5 mL, 1.5 mmol, 3

equiv) to deliver the allylic alcohol **11c** ($C_{30}H_{56}O_5Si_2$, 552.94 g/mol, 0.26 g, 0.47 mmol, 95%) as a colorless oil; $R_f$ = 0.57 (hexanes–EtOAc, 2:1); $[\alpha]_D^{25}$ not determined.

IR (film): 3000–2850, 1515, 1250, 835 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = −0.04 (s, 3 H), 0.00 (s, 3 H), 0.01 (s, 3 H), 0.04 (s, 3 H), 0.66 (d, *J* = 7.3 Hz, 3 H), 0.85 (s, 9 H), 0.86 (s, 9 H), 1.56 (s, 3 H), 1.85–1.90 (m, 1 H), 2.27–2.30 (m, 1 H), 3.40 (dd, *J* = 9.4, 7.9 Hz, 1 H), 3.49 (dd, *J* = 9.9, 7.4 Hz, 1 H), 3.54 (dd, *J* = 9.7, 5.7 Hz, 1 H), 3.69 (dd, *J* = 9.9, 4.9 Hz, 1 H), 3.78 (s, 3 H), 3.88 (d, *J* = 8.3 Hz, 1 H), 4.16 (dd, *J* = 6.5, 2.3 Hz, 2 H), 4.33 (d, *J* = 11.5 Hz, 1 H), 4.44 (d, *J* = 11.5 Hz, 1 H), 5.51 (t, *J* = 6.7 Hz, 1 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 7.22 (d, *J* = 7.8 Hz, 2 H); no OH signal detected.

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.2, –4.4, 11.3, 12.0, 18.0, 18.1, 25.8, 35.6, 38.7, 55.1, 59.0, 60.6, 70.2, 72.0, 81.0, 113.5, 125.8, 129.0, 130.9, 140.2, 158.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{56}O_5Si_2Na$: 575.3559; found: 575.3549.

### Diene 7e by Julia–Kocienski Olefination of 11b (Scheme 6)

*$MnO_2$ Oxidation*: To a solution of the allylic alcohol **11b** ($C_{29}H_{54}O_4Si_2$, 522.92 g/mol, 0.3 g, 0.574 mmol, 1 equiv) in $CH_2Cl_2$ (12 mL) was added $MnO_2$ (86.94 g/mol, 0.59 g, 6.78 mmol, 12 equiv) and the mixture was stirred in the dark at 40 °C for 3 h. The mixture was then filtered through Celite and the filter cake was rinsed with $CH_2Cl_2$. The combined filtrates were concentrated in vacuo to afford the corresponding enal that was used immediately and without further purification; $R_f$ = 0.51 (hexanes–EtOAc, 10:1).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = –0.05 (s, 3 H), 0.00 (s, 6 H), 0.05 (s, 3 H), 0.75 (d, *J* = 7.3 Hz, 3 H), 0.84 (s, 9 H), 0.89 (s, 9 H), 2.00–2.05 (m, 1 H), 2.08 (s, 3 H), 2.19–2.22 (m, 1 H), 3.41 (dd, *J* = 8.8, 8.8 Hz, 1 H), 3.50 (dd, *J* = 9.9, 7.7 Hz, 1 H), 3.54 (dd, *J* = 9.5, 5.3 Hz, 1 H), 3.71 (dd, *J* = 9.9, 5.3 Hz, 1 H), 4.05 (d, *J* = 7.3 Hz, 1 H), 4.41 (d, *J* = 12.0 Hz, 1 H), 4.50 (d, *J* = 12.0 Hz, 1 H), 5.98 (d, *J* = 8.0 Hz, 1 H), 7.24–7.31 (m, 5 H), 10.00 (d, *J* = 8.0 Hz, 1 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.2, –4.6, 12.1, 12.9, 18.0, 18.1, 25.7, 25.8, 35.8, 39.0, 60.7, 70.3, 72.6, 80.7, 127.3, 127.4, 127.5, 128.2, 138.6, 163.8, 191.3.

*Julia–Kocienski Olefination*: To a solution of (*R*)-**12** ($C_{14}H_{20}N_4O_2S$, 308.40 g/mol, 0.321 g, 1.041 mmol, 1.8 equiv) in THF (6 mL) at –78 °C was added KHMDS (0.5 M in toluene, 2.1 mL, 1.05 mmol, 1.8 equiv). After stirring at –78 °C for 30 min, a solution of the above crude enal (0.58 mmol) in THF (12 mL) was added and the mixture was allowed to warm to r.t. overnight. The reaction mixture was then diluted by the addition of sat. aq $NH_4Cl$ (15 mL), The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1) to afford the tris-protected (2*R*,3*R*,4*R*,5*E*,7*E*,9*R*)-2-(hydroxymethyl)-3,5,9-trimethyltrideca-5,7-diene-1,4-diol **7e** ($C_{36}H_{66}O_3Si_2$, 603.09 g/mol, 0.26 g, 0.431 mmol, 75%, *E*/*Z* >95:5) as a colorless oil; $R_f$ = 0.6 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ –11.8 (*c* 1.08, $CHCl_3$).

IR (film): 3000–2850, 1470, 1255, 1090, 835 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = –0.07 (s, 3 H), 0.01 (s, 3 H), 0.00 (s, 3 H), 0.02 (s, 3 H), 0.67 (d, *J* = 7.3 Hz, 3 H), 0.85 (s, 9 H), 0.86 (m, 12 H), 0.98 (d, *J* = 6.5 Hz, 3 H), 1.23–1.27 (m, 6 H), 1.62 (s, 3 H), 1.90–1.94 (m, 1 H), 2.11–2.15 (m, 1 H), 2.31–2.33 (m, 1 H), 3.45 (dd, *J* = 9.2, 7.9 Hz, 1 H), 3.49 (dd, *J* = 9.5, 7.5 Hz, 1 H), 3.59 (dd, *J* = 9.5, 5.5 Hz, 1 H), 3.72 (dd, *J* = 9.8, 4.8 Hz, 1 H), 3.66 (d, *J* = 8.3 Hz, 1 H), 4.41 (d, *J* = 12.1 Hz, 1 H), 4.52 (d, *J* = 12.0 Hz, 1 H), 5.47 (dd, *J* = 15.1, 7.8 Hz, 1 H), 5.86 (d, *J* = 11.0 Hz, 1 H), 6.13 (dd, *J* = 15.1, 11.0 Hz, 1 H), 7.26–7.31 (m, 5 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.3, –4.6, 11.8, 12.0, 14.0, 18.0, 18.1, 20.4, 22.8, 25.8, 25.9, 29.5, 35.9, 36.7, 36.8, 39.0, 60.6, 70.6, 72.4, 81.4, 123.9, 127.0, 127.2, 127.4, 128.1, 136.3, 138.9, 140.1.

Anal. Calcd for $C_{36}H_{66}O_3Si_2$: C, 71.70; H, 11.03. Found: C, 71.6; H, 10.7.

### Diene 7d by Julia–Kocienski Olefination (Scheme 6)

*$MnO_2$ Oxidation*: According to the procedure reported for the preparation of **7e**, the allylic alcohol **11b** ($C_{29}H_{54}O_4Si_2$, 522.92 g/mol, 0.2 g, 0.383 mmol, 1 equiv) in $CH_2Cl_2$ (12 mL) was treated with $MnO_2$ (86.94 g/mol, 0.39 g, 4.49 mmol, 12 equiv) to yield the corresponding enal as a light yellow oil that was used immediately and without further purification; $R_f$ = 0.51 (hexanes–EtOAc, 10:1).

For NMR data of the enal, see above.

*Julia–Kocienski Olefination*: Following the procedure outlined for the synthesis of **7e**, (*S*)-**12** ($C_{14}H_{20}N_4O_2S$, 308.40 g/mol, 0.2 g, 0.649 mmol, 1.8 equiv) in THF (4 mL) was treated with KHMDS (0.5 M in toluene, 1.3 mL, 0.65 mmol, 1.8 equiv) and a solution of the above crude enal (0.37 mmol) in THF (8 mL) to afford **7d** ($C_{36}H_{66}O_3Si_2$, 603.09 g/mol, 174 mg, 0.289 mmol, 75%, *E*/*Z* >95:5) as a colorless oil; $R_f$ = 0.57 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ +8.8 (*c* 1.18, $CHCl_3$).

IR (film): 3000–2850, 1470, 1255, 1090, 835 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = –0.07 (s, 3 H), –0.01 (s, 3 H), 0.00 (s, 3 H), 0.02 (s, 3 H), 0.66 (d, *J* = 7.3 Hz, 3 H), 0.84 (s, 9 H), 0.84–0.87 (m, 12 H), 0.97 (d, *J* = 6.5 Hz, 3 H), 1.20–1.30 (m, 6 H), 1.61 (s, 3 H), 1.90–1.96 (m, 1 H), 2.10–2.15 (m, 1 H), 2.30–2.33 (m, 1 H), 3.45 (dd, *J* = 8.8, 8.0 Hz, 1 H), 3.49 (dd, *J* = 9.8, 7.5 Hz, 1 H), 3.58 (dd, *J* = 9.8, 5.5 Hz, 1 H), 3.71 (dd, *J* = 9.8, 4.8 Hz, 1 H), 3.86 (d, *J* = 8.5 Hz, 1 H), 4.41 (d, *J* = 12.1 Hz, 1 H), 4.51 (d, *J* = 12.0 Hz, 1 H), 5.46 (dd, *J* = 14.8, 7.8 Hz, 1 H), 5.85 (d, *J* = 10.8 Hz, 1 H), 6.14 (dd, *J* = 14.9, 10.7 Hz, 1 H), 7.26–7.31 (m, 5 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.3, –4.6, 11.6, 12.0, 14.0, 18.0, 18.1, 20.5, 22.7, 25.8, 25.9, 29.5, 35.8, 36.3, 36.7, 36.9, 60.6, 70.5, 72.4, 81.4, 124.0, 127.0, 127.2, 127.4, 128.1, 136.4, 138.9, 140.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{66}O_3Si_2Na$: 625.4443; found: 625.4438.

Anal. Calcd for $C_{36}H_{66}O_3Si_2$: C, 71.70; H, 11.03. Found: C, 71.0; H, 10.6.

### Diene 7e by Julia–Kocienski Olefination (Scheme 6)

*$MnO_2$ Oxidation*: According to the procedure reported for the preparation of **7d**, the allylic alcohol **11c** ($C_{30}H_{56}O_5Si_2$, 552.94 g/mol, 0.26 g, 0.47 mmol, 1 equiv) in $CH_2Cl_2$ (mL) was treated with $MnO_2$ (86.94 g/mol, 0.48 g, 5.52 mmol, 12 equiv) to yield the corresponding enal as a light yellow oil that was used immediately and without further purification; $R_f$ = 0.66 (hexanes–EtOAc, 5:1).

*Julia–Kocienski Olefination*: Following the procedure outlined for the synthesis of **7d**, (*R*)-**12** ($C_{14}H_{20}N_4O_2S$, 308.40 g/mol, 0.24 g, 0.778 mmol, 1.8 equiv) in THF (8 mL) was treated with KHMDS (0.5 M in toluene, 1.5 mL, 0.75 mmol, 1.8 equiv) and a solution of the above crude enal (0.43 mmol) in THF (4 mL) to afford **7e** ($C_{37}H_{68}O_4Si_2$, 633.12 g/mol, 173 mg, 0.273 mmol, 58%, *E*/*Z* = 95:5) as a colorless oil; $R_f$ = 0.36 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ not determined.

IR (film): 3000–2850, 1515, 1250, 1090, 835 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = –0.07 (s, 3 H), 0.00 (s, 3 H), 0.01 (s, 3 H), 0.02 (s, 3 H), 0.65 (d, *J* = 7.3 Hz, 3 H), 0.83 (s, 9 H), 0.84–0.87 (m, 12 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 1.24–1.28 (m, 6 H), 1.61 (s, 3 H), 1.89–1.93

(m, 1 H), 2.10–2.15 (m, 1 H), 2.28–2.32 (m, 1 H), 3.41 (dd, *J* = 9.5, 8.0 Hz, 1 H), 3.48 (dd, *J* = 9.8, 7.5 Hz, 1 H), 3.56 (dd, *J* = 9.7, 5.7 Hz, 1 H), 3.71 (dd, *J* = 9.9, 4.6 Hz, 1 H), 3.78 (s, 3 H), 3.86 (d, *J* = 8.3 Hz, 1 H), 4.33 (d, *J* = 11.5 Hz, 1 H), 4.41 (d, *J* = 11.5 Hz, 1 H), 5.48 (dd, *J* = 15.1, 7.8 Hz, 1 H), 5.85 (d, *J* = 10.5 Hz, 1 H), 6.13 (dd, *J* = 15.1, 10.5 Hz, 1 H), 6.84 (d, *J* = 8.5 Hz, 2 H), 7.23 (d, *J* = 8.5 Hz, 2 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.6, –5.5, –5.2, –4.5, 11.7, 11.9, 14.0, 18.0, 18.1, 20.4, 22.7, 25.8, 25.9, 29.4, 35.8, 36.7, 36.8, 38.8, 55.1, 60.6, 70.2, 71.9, 81.4, 113.5, 123.9, 127.0, 129.0, 131.0, 136.3, 140.1, 158.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{37}H_{68}O_3Si_2Na$: 655.4548; found: 655.4544.

### (*S*)-4-Isopropyl-3-[(*S*)-2-methylhexanoyl]oxazolidin-2-one (18) (Scheme 7)

To a solution of (*S*)-3-hexanoyl-4-isopropyloxazolidin-2-one (**17**; $C_{12}H_{21}NO_3$, 227.30 g/mol, 11.6 g, 51.03 mmol, 1 equiv) in THF (100 mL) at –78 °C was added NaHMDS (2 M in toluene, 31 mL, 62 mmol, 1.2 equiv). The mixture was stirred at –78 °C for 1 h. MeI (141.94 g/mol, 2.27 g/mol, 8 mL, 18.16 g, 127.9 mmol, 2.5 equiv) was added at –78 °C and the reaction mixture was allowed to warm to –20 °C over a period of about 3 h. The reaction mixture was then diluted by the addition of sat. aq $NH_4Cl$ (50 mL). The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 20:1) to yield **18** ($C_{13}H_{23}NO_3$, 241.33 g/mol, 11.4 g, 47.24 mmol, 93%, dr >95:5) as a colorless oil; $R_f$ = 0.5 (hexanes–EtOAc, 10:1); $[\alpha]_D^{25}$ +96.4 (*c* 1.0, $CHCl_3$) {Lit.[32] $[\alpha]_D^{25}$ +79.0 (*c* 1.0, $CHCl_3$). The assignment of the absolute configuration rests on the accepted stereochemical model.

IR (film): 3000–2870, 1780, 1700, 1385, 1200 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.84–0.90 (m, 9 H), 1.17 (d, *J* = 6.8 Hz, 3 H), 1.20–1.40 (m, 5 H), 1.65–1.74 (m, 1 H), 2.29–2.37 (m, 1 H), 3.66–3.74 (m, 1 H), 4.17 (dd, *J* = 9.0, 3.0 Hz, 1 H), 4.24 (dd, *J* = 9.0, 9.0 Hz, 1 H), 4.41–4.45 (m, 1 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 14.0, 14.7, 17.9, 22.7, 28.4, 29.5, 32.8, 37.7, 58.4, 63.2, 153.7, 177.3.

Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.9; H, 9.5; N, 5.5.

### (–)-(*S*)-2-Methylhexan-1-ol (19) (Scheme 7)

To an ice-cooled solution of the 3-(2-methylhexanoyl)oxazolidin-2-one (**18**; $C_{13}H_{23}NO_3$, 241.33 g/mol, 1.82 g, 7.54 mmol, 1 equiv) and MeOH (32.04 g/mol, 0.79 g/mL, 0.9 mL, 711 mg, 22.19 mmol, 3 equiv) in $Et_2O$ (75 mL) was added $LiBH_4$ (21.78 g/mol, 0.49 g, 22.6 mmol, 3 equiv). The cooling bath was removed and the mixture was stirred at r.t. for 1.5 h. The reaction mixture was diluted by the addition of sat. aq Na/K tartrate (40 mL) and subsequently stirred at r.t. for 30 min. The biphasic mixture was then partitioned in a separatory funnel and the aqueous layer was extracted with $Et_2O$ (4 × 30 mL). The combined organic phases were dried ($MgSO_4$) and carefully concentrated at reduced pressure (40 °C/700 mbar). The residue was purified by Kugelrohr distillation (100 °C/20 mbar) to yield, as the distillate, the colorless liquid alcohol **19** ($C_7H_{16}O$, 116.20 g/mol, 0.79 g, 6.8 mmol, 90%) and residual (*S*)-4-isopropyloxazolidin-2-one ($C_6H_{11}NO_2$, 129.16 g/mol, 0.89 g, 6.89 mmol, 91%); $R_f$ = 0.31 (hexanes–EtOAc, 5:1); $[\alpha]^{25}_D$ –13.1 (*c* 1.0, $CHCl_3$) {Lit.[47] $[\alpha]_D^{25}$ –14.2 (*c* 0.31, MeOH), Lit.[48] $[\alpha]_D^{19}$ –11.6 (*c* 7.59, $Et_2O$)}.

IR (film): 3700–3100, 3000–2850, 1465, 1260 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 1.04–1.12 (m, 1 H), 1.19–1.40 (m, 6 H), 1.53–1.62 (m, 1 H), 3.39 (dd, *J* = 10.5, 6.5 Hz, 1 H), 3.48 (dd, *J* = 10.5, 5.8 Hz, 1 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 14.0, 16.5, 22.9, 29.1, 32.7, 35.6, 68.3.

HRMS (EI): *m*/*z* calcd for $[C_7H_{16}O]^+$: 116.1196; found: 116.1177.

### (*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate (20) by Esterification of (*S*)-2-Methylhexan-1-ol (19) (Scheme 7)

To a solution of (*S*)-2-methylhexan-1-ol (**19**; $C_7H_{16}O$, 116.20 g/mol, 20 mg, 0.172 mmol, 1 equiv) in $CH_2Cl_2$ (3 mL) at r.t. was added (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid ($C_{10}H_9F_3O_3$, 234.17 g/mol, 121 mg, 0.517 mmol, 3 equiv), DMAP (122.17 g/mol, 10 mg, 0.082 mmol, 0.5 equiv), and DCC ($C_{13}H_{22}N_2$, 206.33 g/mol, 133 mg, 0.645 mmol, 3.75 equiv). After stirring at r.t. for 3 h, the mixture was diluted by the addition of brine (1 mL). The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 3 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 200:1 to 100:1) to yield the ester **20** ($C_{17}H_{23}F_3O_3$, 332.36 g/mol, 57 mg, 0.172 mmol, 99%, dr >95:5) as a colorless oil; $R_f$ = 0.60 (hexanes–EtOAc, 20:1). The characterization rests on NMR spectroscopy only.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.2 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 1.10–1.31 (m, 6 H), 1.79–1.84 (m, 1 H), 3.53 (s, 3 H), 4.13 (d, *J* = 5.8 Hz, 2 H), 7.37–7.39 (m, 3 H), 7.48–7.50 (m, 2 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 13.9, 16.7, 22.7, 28.8, 32.3, 32.6, 55.3, 71.1, 84.7 (d, $J_{C,F}$ = 28.2 Hz), 121.8, 124.7, 127.4, 128.3, 129.5, 132.2, 166.6.

### (*S*)-5-[(2-Methylhexyl)thio]-1-phenyl-1*H*-tetrazole (21) by Mitsunobu Reaction (Scheme 7)

To an ice-cooled solution of (*S*)-2-methylhexan-1-ol (**19**; $C_7H_{16}O$, 116.20 g/mol, 1 g, 8.605 mmol, 1 equiv) in THF (9 mL) were successively added $PPh_3$ (262.29 g/mol, 2.73 g, 10.41 mmol, 1.2 equiv), 1-phenyl-1*H*-tetrazole-5-thiol (178.21 g/mol, 2.31 g, 12.96 mmol, 1.5 equiv), and diisopropyl azodicarboxylate (202.21 g/mol, 1.027 g/mL, 2.2 mL, 2.26 g, 11.176 mmol, 1.3 equiv). After stirring at 0 °C for 1 h, the mixture was diluted by the addition of sat. aq $NaHCO_3$ (5 mL). The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 50:1) to provide the sulfide **21** ($C_{14}H_{20}N_4S$, 276.40 g/mol, 2.4 g, 8.683 mmol, 99%) as a light yellow oil; $R_f$ = 0.26 (hexanes–EtOAc, 10:1); $[\alpha]_D^{25}$ +3.4 (*c* 1.75, $CHCl_3$).

IR (film): 3000–2850, 1500, 1385 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 1.21–1.33 (m, 5 H), 1.42–1.51 (m, 1 H), 1.88–1.95 (m, 1 H), 3.24 (dd, *J* = 12.6, 7.5 Hz, 1 H), 3.44 (dd, *J* = 12.6, 5.8 Hz, 1 H), 7.51–7.58 (m, 5 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 13.9, 19.0, 22.7, 28.9, 32.8, 35.5, 40.4, 123.7, 129.7, 130.0, 133.6, 154.7.

HRMS (ESI): *m*/*z* calcd for $[C_{14}H_{21}N_4S]^+$: 277.1482; found: 277.1476.

### (*S*)-5-[(2-Methylhexyl)sulfonyl)-1-phenyl-1*H*-tetrazole [(*S*)-12] by Oxidation (Scheme 7)

To an ice-cooled solution of the sulfide **21** ($C_{14}H_{20}N_4S$, 276.40 g/mol, 2.2 g, 7.959 mmol, 1 equiv) in EtOH (78 mL) was added a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (1235.99 g/mol, 100 mg, 0.0809 mmol, 0.01

equiv) in $H_2O_2$ (34.02 g/mol, 7.6 mL of a 30% m/v $H_2O$, 1.11 g/mL, 2.53 g, 74.37 mmol, 9 equiv). The cooling bath was removed and the mixture was stirred at r.t. for 15 h. The reaction mixture was then diluted by the addition of brine (10 mL). The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1 to 50:1) to deliver the sulfone (*S*)-**12** ($C_{14}H_{20}N_4O_2S$, 308.40 g/mol, 2.3 g, 7.458 mmol, 94%) as a light yellow oil; $R_f$ = 0.66 (hexanes–EtOAc, 5:1); $[\alpha]_D^{25}$ –2.1 (*c* 1.01, $CHCl_3$).

IR (film): 3000–2900, 2360–2340, 1500, 1340, 1150, 760 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 3 H), 1.14 (d, *J* = 6.8 Hz, 3 H), 1.22–1.38 (m, 5 H), 1.50–1.56 (m, 1 H), 2.27–2.35 (m, 1 H), 3.56 (dd, *J* = 14.4, 7.9 Hz, 1 H), 3.79 (dd, *J* = 14.4, 4.8 Hz, 1 H), 7.57–7.68 (m, 5 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 13.9, 19.7, 22.5, 28.2, 28.4, 36.2, 61.8, 125.1, 129.6, 131.4, 133.1, 154.0.

HRMS (ESI): *m*/*z* calcd for $[C_{14}H_{21}N_4SO_2]^+$: 309.1380; found: 309.1377.

### Alcohol 7g by Regioselective Silyl Ether Cleavage (Scheme 8)

To a solution of **7e** ($C_{36}H_{66}O_3Si_2$, 603.09 g/mol, 0.26 g, 0.431 mmol, 1 equiv) in THF (4 mL) at 0 °C was slowly added a solution of commercially available HF-pyridine (0.9 mL), pyridine (1.4 mL), and THF (4 mL). The cooling bath was removed and the mixture was stirred at r.t. overnight. The reaction mixture was then diluted by the addition of sat. aq $NaHCO_3$ (6 mL), The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 50:1 to 20:1) to deliver the alcohol **7g** ($C_{30}H_{52}O_3Si$, 488.83 g/mol, 200 mg, 0.409 mmol, 95%) as a colorless oil; $R_f$ = 0.49 (hexanes–EtOAc, 5:1); $[\alpha]_D^{25}$ –23.9 (*c* 0.99, $CHCl_3$).

IR (film): 3000–2850, 1455, 1250, 1050, 835 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = –0.03 (s, 3 H), 0.06 (s, 3 H), 0.77 (d, *J* = 7.3 Hz, 3 H), 0.85 (t, *J* = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 1.20–1.30 (m, 6 H), 1.61 (s, 3 H), 1.86–1.91 (m, 1 H), 2.11–2.15 (m, 1 H), 2.31–2.35 (m, 1 H), 3.38–3.63 (m, 4 H), 3.87 (d, *J* = 6.5 Hz, 1 H), 4.44 (d, *J* = 12.1 Hz, 1 H), 4.48 (d, *J* = 12.1 Hz, 1 H), 5.50 (dd, *J* = 15.1, 7.8 Hz, 1 H), 5.92 (d, *J* = 10.8 Hz, 1 H), 6.13 (dd, *J* = 15.1, 10.8 Hz, 1 H), 7.26–7.34 (m, 5 H); no OH signal detected.

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = –5.3, –4.7, 12.7, 12.8, 14.0, 18.2, 20.4, 22.7, 25.8, 29.5, 36.3, 36.7, 36.9, 39.2, 61.8, 72.8, 73.2, 81.1, 123.6, 127.1, 127.4, 127.5, 128.3, 134.9, 138.1, 140.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{52}O_3SiNa$: 511.3578; found: 511.3571.

### Alcohol 7h by Regioselective Silyl Ether Cleavage (Scheme 8)

In analogy to the procedure reported for the preparation of **7g** from **7e**, **7f** ($C_{37}H_{68}O_4Si_2$, 633.12 g/mol, 140 mg, 0.221 mmol, 1 equiv) in THF (4.5 mL) was subjected to commercially available HF-pyridine (0.44 mL), pyridine (0.7 mL), and THF (4.5 mL) to deliver the alcohol **7h** ($C_{31}H_{54}O_4Si$, 518.85 g/mol, 91 mg, 0.175 mmol, 79%) as a colorless oil; $R_f$ = 0.43 (hexanes–EtOAc, 5:1); $[\alpha]_D^{25}$ –25.0 (*c* 1.4, $CHCl_3$).

IR (film): 3000–2850, 1513, 1250, 1050, 835 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = –0.03 (s, 3 H), 0.05 (s, 3 H), 0.75 (d, *J* = 7.3 Hz, 3 H), 0.85 (t, *J* = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 1.23–1.27 (m, 6 H), 1.60 (s, 3 H), 1.84–1.87 (m, 1 H), 2.09–2.16 (m, 1 H), 2.29–2.32 (m, 1 H), 3.37 (dd, *J* = 9.3, 6.0 Hz, 1 H), 3.41–3.49 (m, 2 H), 3.50–3.54 (m, 1 H), 3.56–3.61 (m, 1 H), 3.78 (s, 3 H), 3.85 (d, *J* = 6.5 Hz, 1 H), 4.37 (d, *J* = 11.8 Hz, 1 H), 4.41 (d, *J* = 11.8 Hz, 1 H), 5.50 (dd, *J* = 15.1, 7.8 Hz, 1 H), 5.90 (d, *J* = 11.0 Hz, 1 H), 6.12 (dd, *J* = 15.1, 11.0 Hz, 1 H), 6.84 (d, *J* = 6.8 Hz, 2 H), 7.20 (d, *J* = 6.8 Hz, 2 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = –5.3, –4.7, 12.7, 12.8, 14.0, 18.2, 20.4, 22.7, 25.7, 29.5, 36.3, 36.7, 36.9, 39.1, 55.2, 61.9, 72.5, 73.0, 81.1, 113.6, 123.6, 127.1, 129.2, 130.1, 134.8, 140.7, 159.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{31}H_{54}O_4SiNa$: 541.3684; found: 541.3683.

### Alkyne 22a by Alcohol to Alkyne Homologation (Scheme 8)

*Dess–Martin Oxidation*: To an ice-cooled solution of the alcohol **7g** ($C_{30}H_{52}O_3Si$, 488.83 g/mol,0.21 g, 0.430 mmol, 1 equiv) in $CH_2Cl_2$ (9 mL) and pyridine (0.9 mL) was added the Dess–Martin periodinane (424.14 g/mol, 0.55 g, 1.297 mmol, 3 equiv). The cooling bath was removed and the mixture was stirred for 3 h at r.t. The reaction mixture was then diluted by the addition of sat. aq $Na_2S_2O_3$ (4 mL). The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 50:1) to provide the corresponding aldehyde as colorless oil. The aldehyde was used immediately and without further purification; $R_f$ = 0.66 (hexanes–EtOAc, 5:1).

$^1H$ NMR (400 MHz, $CDCl_3$): δ = –0.07 (s, 3 H), –0.01 (s, 3 H), 0.85 (m, 15 H), 0.98 (d, *J* = 6.5 Hz, 3 H), 1.23–1.31 (m, 6 H), 1.61 (s, 3 H), 2.10–2.15 (m, 1 H), 2.18–2.45 (m, 1 H), 2.81–2.92 (m, 1 H), 3.54 (dd, *J* = 9.5, 6.3 Hz, 1 H), 3.83 (dd, *J* = 9.5, 7.8 Hz, 1 H), 3.88 (d, *J* = 6.8 Hz, 1 H), 4.46 (d, *J* = 12.3 Hz, 1 H), 4.50 (d, *J* = 12.1 Hz, 1 H), 5.50 (dd, *J* = 14.9, 7.7 Hz, 1 H), 5.94 (d, *J* = 10.8 Hz, 1 H), 6.12 (dd, *J* = 14.8, 10.8 Hz, 1 H), 7.25–7.34 (m, 5 H), 9.78 (d, *J* = 1.3 Hz, 1 H).

*Chloromethylenation*: To an ice-cooled suspension of $ClCH_2PPh_3Cl$ (347.22 g/mol, 0.91 g, 2.621 mmol, 6 equiv) in THF (4 mL) was added *n*-BuLi (2.2 M in *n*-hexane, 1 mL, 2.2 mmol, 5 equiv). The cooling bath was removed and the red-brown mixture was stirred at r.t. for 2 h. The mixture was chilled to 0 °C and a solution of the above crude aldehyde ($C_{30}H_{50}O_3Si$, 486.81 g/mol, 214 mg, 0.44 mmol, 1 equiv) in THF (4 mL) was added. After stirring at 0 °C for 5 min, the reaction mixture was diluted by the addition of pentane (18 mL) and the solids were removed by filtration through a plug of silica gel. The filter cake was thoroughly rinsed with pentane and the combined filtrates were concentrated in vacuo to yield a residue that was used without further purification; $R_f$ = 0.66 (hexanes–EtOAc, 20:1).

*β-Elimination*: To a solution of LDA, prepared from *i*-$Pr_2NH$ (101.19 g/mol, 0.722 g/mL, 0.22 mL, 158.8 mg, 1.569 mmol, 3.6 equiv) and *n*-BuLi (2.2 M in *n*-hexane, 0.7 mL, 1.54 mmol, 3.5 equiv), in THF (4 mL) at –78 °C was added a cooled (–78 °C) solution of the above vinyl chloride (assumed 0.44 mmol, 1 equiv) in THF (4 mL). After stirring at –78 °C for 0.5 h and at 0 °C for 1 h, the reaction mixture was diluted by the addition of sat. aq $NH_4Cl$ (4 mL). The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1) to yield the bis-protected (2*S*,3*R*,4*R*,5*E*,7*E*,9*R*)-2-ethynyl-3,5,9-trimethyltrideca-5,7-diene-1,4-diol **22a** ($C_{31}H_{50}O_2Si$, 482.82 g/mol, 119 mg, 0.247 mmol, 54%) as a colorless oil; $R_f$ = 0.46 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ –26.9 (*c* 0.92, $CHCl_3$).

IR (film): 3000–2850, 1640, 1055, 835 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = –0.05 (s, 3 H), 0.06 (s, 3 H), 0.65 (d, *J* = 6.8 Hz, 3 H), 0.83–0.86 (m, 12 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 1.23–1.27 (m, 6 H), 1.61 (s, 3 H), 1.84–1.89 (m, 1 H), 2.02 (d, *J* = 2.3 Hz, 1 H),

2.10–2.15 (m, 1 H), 3.32–3.36 (m, 1 H), 3.47 (dd, *J* = 9.2, 9.2 Hz, 1 H), 3.58 (dd, *J* = 9.2, 6.9 Hz, 1 H), 3.83 (d, *J* = 9.8 Hz, 1 H), 4.47 (d, *J* = 12.1 Hz, 1 H), 4.58 (d, *J* = 12.3 Hz, 1 H), 5.51 (dd, *J* = 15.2, 7.9 Hz, 1 H), 5.84 (d, *J* = 10.8 Hz, 1 H), 6.12 (dd, *J* = 14.9, 10.7 Hz, 1 H), 7.25–7.32 (m, 5 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.3, –4.8, 10.6, 11.0, 14.0, 18.1, 20.4, 22.7, 25.8, 29.4, 32.2, 36.1, 36.7, 36.8, 70.9, 71.2, 72.4, 81.3, 82.8, 123.8, 127.5, 127.6, 128.1, 128.3, 135.6, 138.2, 140.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{50}O_2SiNa$: 505.3472; found: 505.3467.

### Alkyne 22b by Alcohol to Alkyne Homologation (Scheme 8)

*Dess–Martin Oxidation*: Following the procedure reported for the oxidation of **7g**, **7h** ($C_{31}H_{54}O_4Si$, 518.85 g/mol, 93 mg, 0.179 mmol, 1 equiv) in $CH_2Cl_2$ (4 mL) and pyridine (0.4 mL) was treated with the Dess–Martin periodinane (424.14 g/mol, 0.23 g, 0.542 mmol, 3 equiv) to provide the corresponding enal as a colorless oil (80 mg) that was used immediately and without further purification; $R_f$ = 0.71 (hexanes–EtOAc, 5:1).

*Chloromethylenation*: According to the procedure used for the preparation of the alkyne **23a**, the above crude aldehyde (assumed 0.155 mmol, 1 equiv) from the Dess–Martin oxidation in THF (4 mL) was treated with the reagent prepared from $ClCH_2PPh_3Cl$ (347.22 g/mol, 0.37 g, 1.066 mmol, 7 equiv) in THF (4 mL) and *n*-BuLi (2.3 M in *n*-hexane, 0.4 mL, 0.92 mmol, 6 equiv) to deliver a residue that was used without further purification; $R_f$ = 0.41 (hexanes–EtOAc, 20:1).

*β-Elimination*: Using the procedure reported for the preparation of alkyne **22a**, the crude vinyl chloride (assumed 0.155 mmol, 1 equiv) from the chloromethylenation in THF (1.6 mL) was treated with LDA, prepared from *i*-$Pr_2NH$ (101.19 g/mol, 0.722 g/mL, 0.07 mL, 50.54 mg, 0.499 mmol, 3.2 equiv) and *n*-BuLi (2.2 M in *n*-hexane, 0.21 mL, 0.462 mmol, 3.0 equiv), in THF (1.6 mL) to deliver the alkyne **22b** ($C_{32}H_{52}O_3Si$, 512.85 g/mol, 41 mg, 0.08 mmol, 45%) as a colorless oil; $R_f$ = 0.41 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ –20.5 (*c* 1.07, $CHCl_3$).

IR (film): 3000–2850, 1615, 1515, 1260, 1055, 835 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = –0.05 (s, 3 H), 0.07 (s, 3 H), 0.65 (d, *J* = 6.8 Hz, 3 H), 0.83–0.86 (m, 12 H), 0.98 (d, *J* = 6.5 Hz, 3 H), 1.24–1.28 (m, 6 H), 1.62 (s, 3 H), 1.83–1.88 (m, 1 H), 2.02 (d, *J* = 2.5 Hz, 1 H), 2.10–2.15 (m, 1 H), 3.31–3.36 (m, 1 H), 3.44 (dd, *J* = 9.4, 9.4 Hz, 1 H), 3.55 (dd, *J* = 9.5, 6.8 Hz, 1 H), 3.78 (s, 3 H), 3.84 (d, *J* = 10.0 Hz, 1 H), 4.40 (d, *J* = 11.8 Hz, 1 H), 4.51 (d, *J* = 11.8 Hz, 1 H), 5.51 (dd, *J* = 15.2, 7.7 Hz, 1 H), 5.84 (d, *J* = 10.5 Hz, 1 H), 6.13 (dd, *J* = 15.2, 10.5 Hz, 1 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 7.25 (d, *J* = 8.8 Hz, 2 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.3, –4.7, 10.6, 11.0, 14.0, 18.1, 20.4, 22.7, 25.8, 29.4, 32.1, 36.0, 36.7, 36.8, 55.1, 70.5, 71.2, 72.0, 81.3, 82.8, 113.6, 123.8, 128.1, 129.2, 130.2, 135.6, 140.6, 159.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{32}H_{52}O_3SiNa$: 535.3578; found: 535.3574.

### Alkyne 23a by Methylation (Scheme 8)

To a solution of LDA, prepared from *i*-$Pr_2NH$ (101.19 g/mol, 0.722 g/mL, 0.1 mL, 72.2 mg, 0.722 mmol, 3.1 equiv) and *n*-BuLi (2.3 M in *n*-hexane, 0.3 mL, 0.69 mmol, 3 equiv), in THF (2 mL) at –78 °C was added a cooled (–78 °C) solution of the alkyne **22a** ($C_{31}H_{50}O_2Si$, 482.82 g/mol, 111 mg, 0.23 mmol, 1 equiv) in THF (4 mL). After stirring for 30 min at –78 °C, MeI (141.94 g/mol, 2.27 g/mol, 0.09 mL, 204.3 mg, 1.439 mmol, 6 equiv) was added and the reaction mixture was allowed to warm to –30 °C. The reaction mixture was then diluted by the addition of sat. aq $NH_4Cl$ (2 mL). The biphasic mixture was partitioned in a separatory funnel and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexanes–EtOAc, 100:1) to yield the bis-protected (2*S*,3*R*,4*R*,5*E*,7*E*,9*R*)-3,5,9-trimethyl-2-(prop-1-yn-1-yl)trideca-5,7-diene-1,4-diol **23a** ($C_{32}H_{52}O_2Si$, 496.85 g/mol, 100 mg, 0.201 mmol, 87%) as a colorless oil; $R_f$ = 0.63 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ –33.6 (*c* 1.07, $CHCl_3$).

IR (film): 3000–2850, 1640, 1055, 835 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = –0.05 (s, 3 H), 0.06 (s, 3 H), 0.60 (d, *J* = 7.0 Hz, 3 H), 0.83–0.86 (m, 12 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 1.23–1.27 (m, 6 H), 1.61 (s, 3 H), 1.78 (d, *J* = 2.3 Hz, 3 H), 1.80–1.86 (m, 1 H), 2.10–2.17 (m, 1 H), 3.25–3.30 (m, 1 H), 3.41 (dd, *J* = 9.4, 9.4 Hz, 1 H), 3.51 (dd, *J* = 9.4, 6.5 Hz, 1 H), 3.81 (d, *J* = 9.8 Hz, 1 H), 4.45 (d, *J* = 12.3 Hz, 1 H), 4.56 (d, *J* = 12.3 Hz, 1 H), 5.49 (dd, *J* = 15.2, 7.8 Hz, 1 H), 5.84 (d, *J* = 10.3 Hz, 1 H), 6.13 (dd, *J* = 15.2, 10.3 Hz, 1 H), 7.25–7.32 (m, 5 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.3, –4.8, 3.5, 10.7, 11.0, 14.0, 18.1, 20.4, 22.8, 25.8, 29.4, 32.2, 36.2, 36.7, 36.8, 71.2, 72.3, 78.4, 81.5, 81.8, 123.9, 127.4, 127.6, 127.9, 128.2, 136.0, 138.4, 140.7.

HRMS (ESI): *m*/*z* calcd for [$C_{32}H_{53}O_2SiNa$]$^+$: 519.3629; found: 519.3623.

### Alkyne 23b by Methylation (Scheme 8)

Following the procedure for the preparation of **23a** from **22a**, **22b** ($C_{32}H_{52}O_3Si$, 512.85 g/mol, 41 mg, 0.08 mmol, 1 equiv) in THF (1.6 mL) was subjected to a solution of LDA in THF (0.8 mL), prepared from *i*-$Pr_2NH$ (101.19 g/mol, 0.722 g/mL, 0.04 mL, 28.9 mg, 0.286 mmol, 3.6 equiv) and *n*-BuLi (2.2 M in *n*-hexane, 0.1 mL, 0.22 mmol, 2.75 equiv), and MeI (141.94 g/mol, 2.27 g/mol, 0.03 mL, 68.1 mg, 0.48 mmol, 6 equiv) to yield **23b** ($C_{33}H_{54}O_3Si$, 526.88 g/mol, 38 mg, 0.072 mmol, 90%) as a colorless oil; $R_f$ = 0.53 (hexanes–EtOAc, 20:1); $[\alpha]_D^{25}$ –31.0 (*c* 0.93, $CHCl_3$).

IR (film): 3000–2850, 1630 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = –0.05 (s, 3 H), 0.06 (s, 3 H), 0.60 (d, *J* = 6.8 Hz, 3 H), 0.83–0.86 (m, 12 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 1.24–1.28 (m, 6 H), 1.62 (s, 3 H), 1.78 (d, *J* = 2.3 Hz, 3 H), 1.80–1.84 (m, 1 H), 2.10–2.16 (m, 1 H), 3.26–3.28 (m, 1 H), 3.38 (dd, *J* = 9.4, 9.4 Hz, 1 H), 3.48 (dd, *J* = 9.4, 6.5 Hz, 1 H), 3.78 (s, 3 H), 3.81 (d, *J* = 9.8 Hz, 1 H), 4.38 (d, *J* = 11.8 Hz, 1 H), 4.50 (d, *J* = 11.8 Hz, 1 H), 5.50 (dd, *J* = 15.1, 7.5 Hz, 1 H), 5.84 (d, *J* = 11.0 Hz, 1 H), 6.13 (dd, *J* = 15.1, 11.0 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 7.25 (d, *J* = 8.0 Hz, 2 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = –5.4, –4.8, 3.5, 10.6, 11.1, 14.0, 18.1, 20.4, 22.7, 25.8, 29.4, 32.1, 36.1, 36.7, 36.8, 55.1, 70.9, 71.9, 77.1, 78.3, 81.5, 113.6, 123.9, 127.9, 129.2, 130.4, 136.0, 140.3, 159.0.

HRMS (ESI): *m*/*z* calcd for [$C_{33}H_{54}O_3SiNa$]$^+$: 549.3734; found: 549.3723.

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## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561614.

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