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Synthesis of chiral hexynones for use as precursors to native photosynthetic hydroporphyrins†

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A planned total synthesis of photosynthetic tetrapyrrole macrocycles installs essential stereochemical features in early precursors *via* established asymmetric methodology. Key building blocks are dihydrodipyrrins that contain a chiral pyrroline unit, for which chiral hex-5-yn-2-ones are valuable precursors. Chiral hex-5-yn-2-ones bearing diverse functional groups at the 1-position were sought that correspond to the chiral pyrroline units (rings B and D) of bacteriochlorophyll *a*. Three main results are reported herein. First, (2*R*,3*R*)-3-ethyl-2-methylpent-4-ynoic acid, prepared *via* a Schreiber-modified Nicholas reaction, was converted to the analogous chiral Weinreb pentynamide. The latter was treated with tributyltin-one-carbon synthons to create a 1-hydroxyhex-5-yn-2-one scaffold containing the two requisite stereocenters and with the newly introduced hydroxy group in free form or protected as the Me, MOM, THP, MEM, Bn, or SEM derivative. Second, improved routes to intermediates on the path to the pre-B compound, (3*R*,4*R*)-1,1-dimethoxy-3-ethyl-4-methylhex-5-yn-2-one, were developed, in part by derivatization of the chiral Weinreb pentynamide. Third, one (semisynthetic) chiral hexynone bearing a native phytyl substituent, a near-universal precursor to ring D of photosynthetic hydroporphyrins, was prepared in 2.5 mmol quantity. The synthesis and manipulation were achieved while maintaining stereochemical integrity in these somewhat densely functionalized chiral hexynones (three functional groups and two stereocenters in a six-carbon scaffold). Altogether, 22 new compounds have been prepared, including 15 chiral hexynones for studies in (bacterio)chlorophyll synthetic methodology. The chiral hexynones were prepared in quantities ranging from 0.11–12 mmol as required for exploratory and/or preparative studies.

Introduction

Chlorophyll *a* and bacteriochlorophyll *a*, the chief photoactive molecules of oxygenic and anoxygenic photosynthesis, respectively, are chiral molecules (Chart 1).[1–4] The stereocenters are located in the (saturated) pyrroline units, ring E, and in the phytyl chain. Chlorophyll *a* contains one pyrroline unit (ring D; two stereocenters) whereas bacteriochlorophyll *a* contains two pyrroline units (rings B and D; four stereocenters). Both macrocycles also contain a common stereocenter in ring E, but the

relatively facile epimerization at the β-ketoester causes the stereochemical configuration at this site to be self-setting.[5–7] While structural variation occurs across the family of photosynthetic tetrapyrroles,[8] the chiral ring D is invariably identical to that of (bacterio)chlorophyll *a*. The chirality of the macrocycles presents challenges to synthesis.

A retrosynthesis[9] for bacteriochlorophyll *a* is shown in Scheme 1: stereochemically defined AD (**I**) and BC (**II**)[10] halves undergo Knoevenagel condensation followed by double-ring closure, which entails Nazarov cyclization (to form ring E), electrophilic aromatic substitution (S$_E$Ar), and elimination of methanol. The incorporation of phytol and magnesium completes the synthesis. The macrocycle-forming strategy has been demonstrated with chemically robust, *gem*-dimethyl-substituted dihydrodipyrrins (both AD and BC halves)[11] and extended to use of a model *trans*-dialkyl-substituted dihydrodipyrrin AD half,[9,12,13] but has not yet been extended to create the native macrocycles. The success of this strategy – where stereochemical features are installed early in the synthesis – requires access to chiral precursors to rings B and D, each of which contains a *trans*-dialkyl-

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† Electronic supplementary information (ESI) available: ^{1}H NMR and ^{13}C{^{1}H} NMR spectra for all new compounds; ^{1}H NMR and ^{13}C{^{1}H} NMR spectra for known compounds **4**, **5-R**, **7**, **18–23**, **Sn-Me**, **Sn-MOM**, **Sn-THP**, **Sn-MEM**, **Sn-Bn**, **Sn-SEM**, and **Sn-(OMe)₂**; single-crystal X-ray diffraction data. CCDC 2287122 (**10**), 2287123 (**11**) and 2287124 (**12**). For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3nj03900e

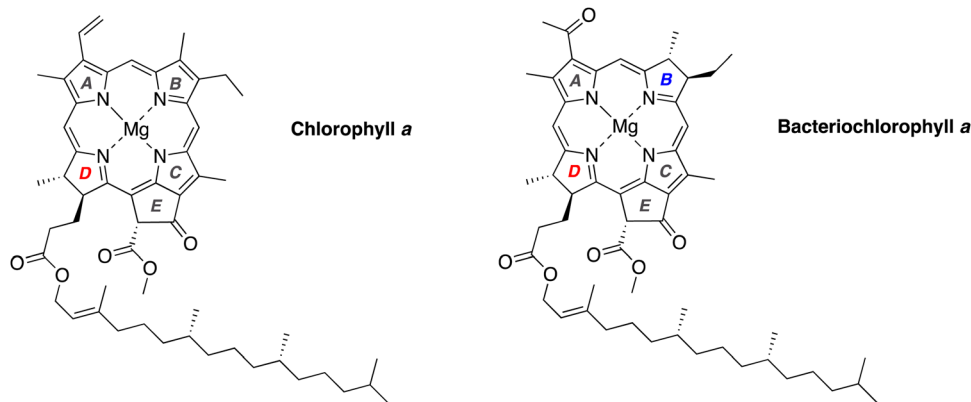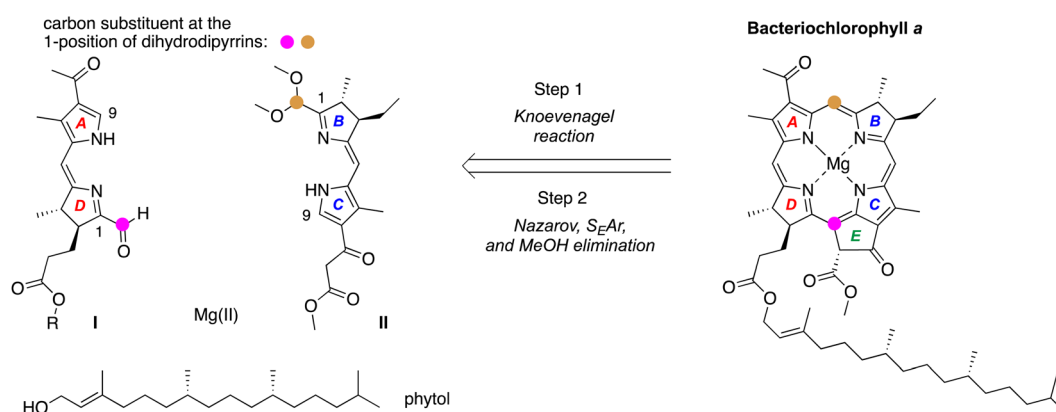‡ Equal contributions by both coauthors.

Chart 1 Key photosynthetic pigments.

Scheme 1 Retrosynthesis of bacteriochlorophyll *a*.

substituted pyrroline ring. The route also requires a one-carbon functional group at the 1-position of each dihydrodipyrrin; moreover, the two groups must be non-identical for selective joining to give the macrocycle. The two groups employed to date are formyl (attached to ring D) and dimethoxymethyl (attached to ring B). The development of access to hydrodipyrrins bearing distinct one-carbon groups at the 1-position – for reaction and protection – is an essential aspect of methodology studies in this domain.[14]

A route for formation of the pyrroline unit concomitantly with the dihydrodipyrrin was developed through extensive work by Jacobi and coworkers (Scheme 2, top).[15–21] The Pd-mediated coupling of a 2-iodopyrrole (**III**) with a chiral pentynoic acid (**IV**) is followed by Petasis methenylation[22] of lactone **V**, hydration and Paal–Knorr ring closure[23,24] of ene-lactone-pyrrole **VI**, and Riley oxidation[25] of dihydrodipyrrin **VII** to afford the dihydrodipyrrin-carboxaldehyde AD half (**VIII**). Two chiral pentynoic acids have been carried through the Jacobi pathway to form dihydrodipyrrins; the structures include R = ethyl (**IVa**)[9,26] and R = 3-(*tert*-butyldiphenylsilyloxy)propyl (**IVb**).[26] The chiral pentynoic acids (**IVa,b**) were prepared by use of the Schreiber-modified Nicholas reaction.[27–31]
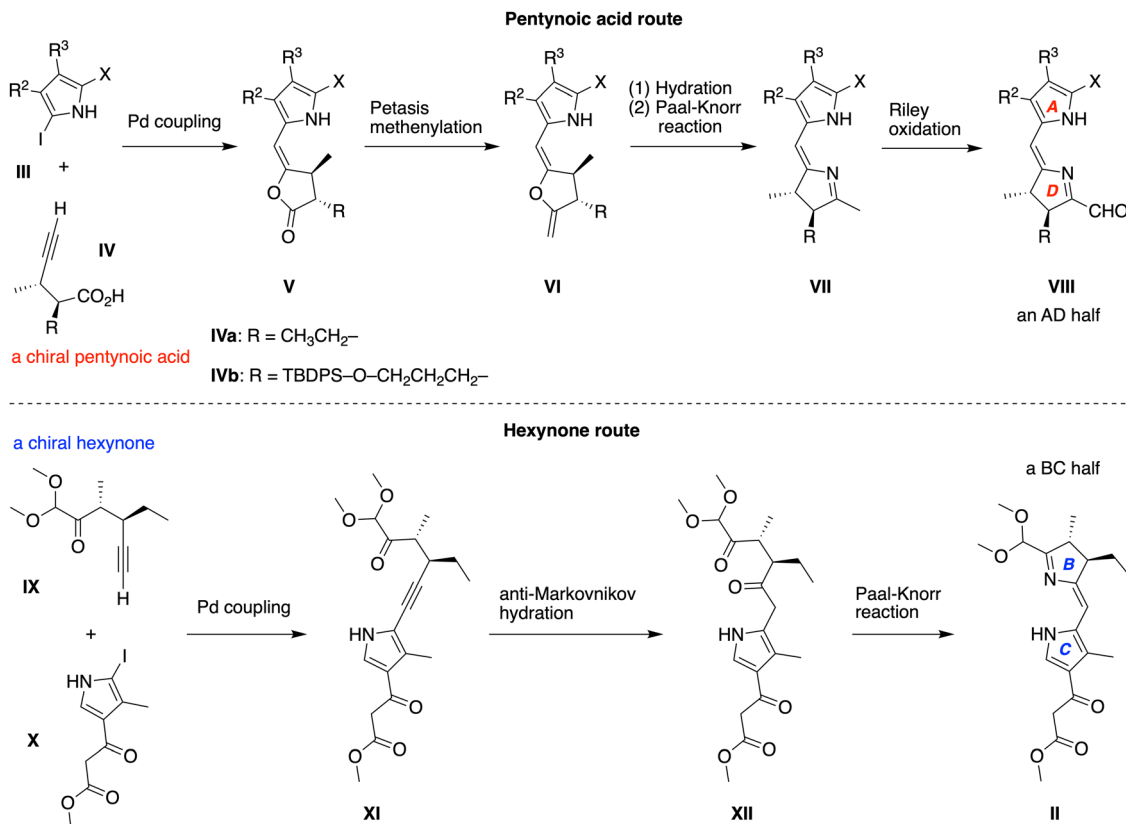
The pentynoic acid route was not viable for the synthesis of the BC half (**II**) of bacteriochlorophyll *a* given the presence of

the β-ketoester unit. A route that sidesteps such problems was developed very recently (Scheme 2, bottom).[10] The route extends the pioneering work of Jacobi with introduction of the following key steps: (1) Sonogashira coupling[32,33] of a chiral hex-5-yn-2-one (**IX**) that bears the requisite 1,1-dimethoxy groups with a 2-iodopyrrole (**X**); (2) anti-Markovnikov hydration[34,35] of the alkyne (**XI**); and (3) Paal–Knorr ring closure of the diketone (**XII**). The stereochemical configuration of chiral hexynone **IX** was also created through use of a Schreiber-modified Nicholas reaction.[27–31] The use of a chiral hexynone, which bears a pre-installed one-carbon moiety, thereby bypasses the Petasis methenylation and Riley oxidation required upon use of a chiral pentynoic acid.

To expand the chemistry for preparing native macrocycles and analogues beyond that accessible *via* the single chiral hexynone (**IX**) heretofore examined, a family of chiral hex-5-yn-2-ones was prepared and is reported herein. Three objectives were sought at the outset of this work.

(1) For fundamental studies of dihydrodipyrrin coupling reactions, chiral hex-5-yn-2-ones were sought that are equipped with distinct reactive handles at the 1-position (Z = hydroxymethyl and diverse protected hydroxymethyl groups, *versus* the 1,1-dimethoxymethyl moiety in **IX**) as is shown in Scheme 3. The 1-position of the chiral hexynone for ring B (or D) gives rise

Scheme 2 Syntheses of chiral dihydrodipyrrins.

to position 5 (or 15) in the macrocycle. The protected hydroxymethyl group at the hexynone 1-position was highly desired to enable isolation of the intermediate following Nazarov cyclization yet still be able to carry out a subsequent macrocyclization process; such interruption of the double-ring closure process was not possible given the reactivity of the 1,1-dimethoxymethyl group under the conditions for the Nazarov cyclization.

(2) A chiral hex-5-yn-2-one was sought that is equipped with the native phytyl propanoate group of ring D (Scheme 3).
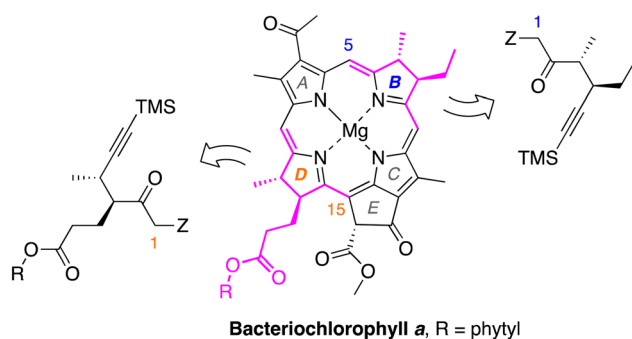
(3) Selected precursors were sought at reasonable scale because an objective is to obtain target photosynthetic tetrapyrroles for diverse studies. The desired scale of target photosynthetic

hydroporphins is ~ 10 μmol, which corresponds to ~ 9 mg of bacteriochlorophyll a (911.5 Da). The quantity of A–D constituents is at least 100 μmol, and the quantity of precursors such as chiral hexynones is at least 1–10 mmol to accommodate losses during multistep syntheses and forays in the pursuit of diverse target compounds. The BC half (**II**) has been prepared at the 0.74 mmol scale (279 mg).[10] Here, a chiral hexynone bearing substituents corresponding to ring D was prepared in a quantity of 2.5 mmol, and eight other chiral hexynones corresponding to ring B and bearing diverse 1-substituents were prepared for fundamental studies. In pursuit of the aforementioned objectives, several improved approaches also emerged that facilitate access to key intermediates on the path to chiral hexynone **IX**, which comprises the pre-B moiety.
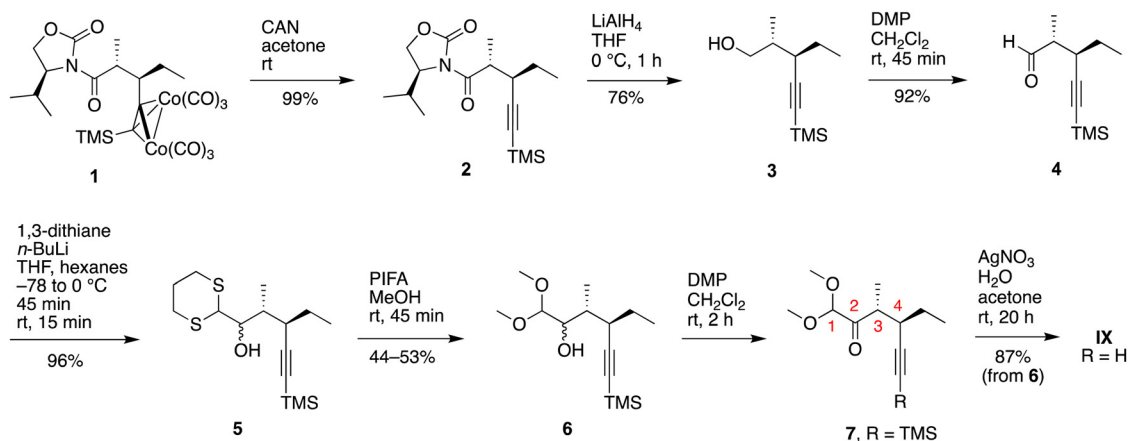
Results and discussion

Reconnaissance

Key features of the recent synthesis of compound **IX**[10] are sketched in Scheme 4. Briefly, the Schreiber-Nicholas adduct **1** (from the Schreiber-modified Nicholas reaction[27–31]) was deprotected with cerium ammonium nitrate (CAN) to give the alkyne **2**, a chiral pentynamide. Reduction of the latter with LiAlH$_4$ gave the corresponding chiral pentynol **3**. Oxidation with Dess–Martin periodinane (DMP) reagent gave the desired chiral pentynal **4**. Addition of 2-lithio-1,3-dithiane gave alcohol **5**, which underwent thia-oxa exchange with methanol in the

Bacteriochlorophyll *a*, R = phytyl

Scheme 3 Rationale for access to diverse chiral hexynones.

Scheme 4 Prior synthesis[10] of chiral hexynone **IX**.

presence of phenyliodine bis(trifluoroacetate) (PIFA) to give **6**. Oxidation of the alcohol with DMP followed by removal of the TMS group with AgNO$_3$ gave the target chiral hex-5-yn-2-one **IX**. The latter constitutes a precursor to ring B of bacteriochlorophyll *a*.

Exploration of the derivatization of Schreiber-Nicholas chiral pentynamide 1

The prior chemistry shown in Scheme 4 afforded chiral hexynone **IX**, the pre-B compound. Here, means to derivatize the chiral pentynamide **1** were sought to gain more direct access to chiral pentynal **4** and to open the door to the formation of diverse chiral, 1-functionalized hex-5-yn-2-ones. The following paths were pursued (Scheme 5).

(1) Direct treatment of Schreiber-Nicholas adduct **1** with diisobutylaluminum hydride (DIBAL-H)[36] gave aldehyde **4-Co** (75% yield). Subsequent deprotection with CAN to obtain the target pentynal **4** was precarious; at room temperature both the aldehyde **4** and the carboxylic acid **8** were obtained. The same process with strict maintenance of the reaction mixture at 0 °C showed only the aldehyde **4** without the carboxylic acid **8**. Aldehyde **4** upon purification was found to spontaneously undergo oxidation to **8** after several hours of exposure to air; hence the compound should be used immediately or stored appropriately under argon at −20 °C at most for a few days (Scheme 5, upper left). In one case, the crude reaction mixture upon treatment with CAN at 0 °C was immediately treated with propane-1,3-dithiol and magnesium bromide etherate[37] to give the dithioacetal of the pentynal (**9**) in 76% yield for the two steps.

(2) Treatment of **2**, which lacks the hexacarbonyldicobalt protection, with DIBAL-H gave selective reduction of the amide exo carbonyl, resulting in the heminal 1′-hydroxyalkyloxazolidin-2-one **10**. The chemoselective origin of the DIBAL-H-induced exo carbonyl reduction[38,39] of *N*-acyloxazolidinones is not clear. Single-crystal X-ray diffraction analysis of **10** showed the (*R*) configuration of the newly generated stereogenic center (Fig. 1). To our knowledge, only one literature report of the stereochemical outcome of such 1′-hydroxyalkyloxazolidin-2-
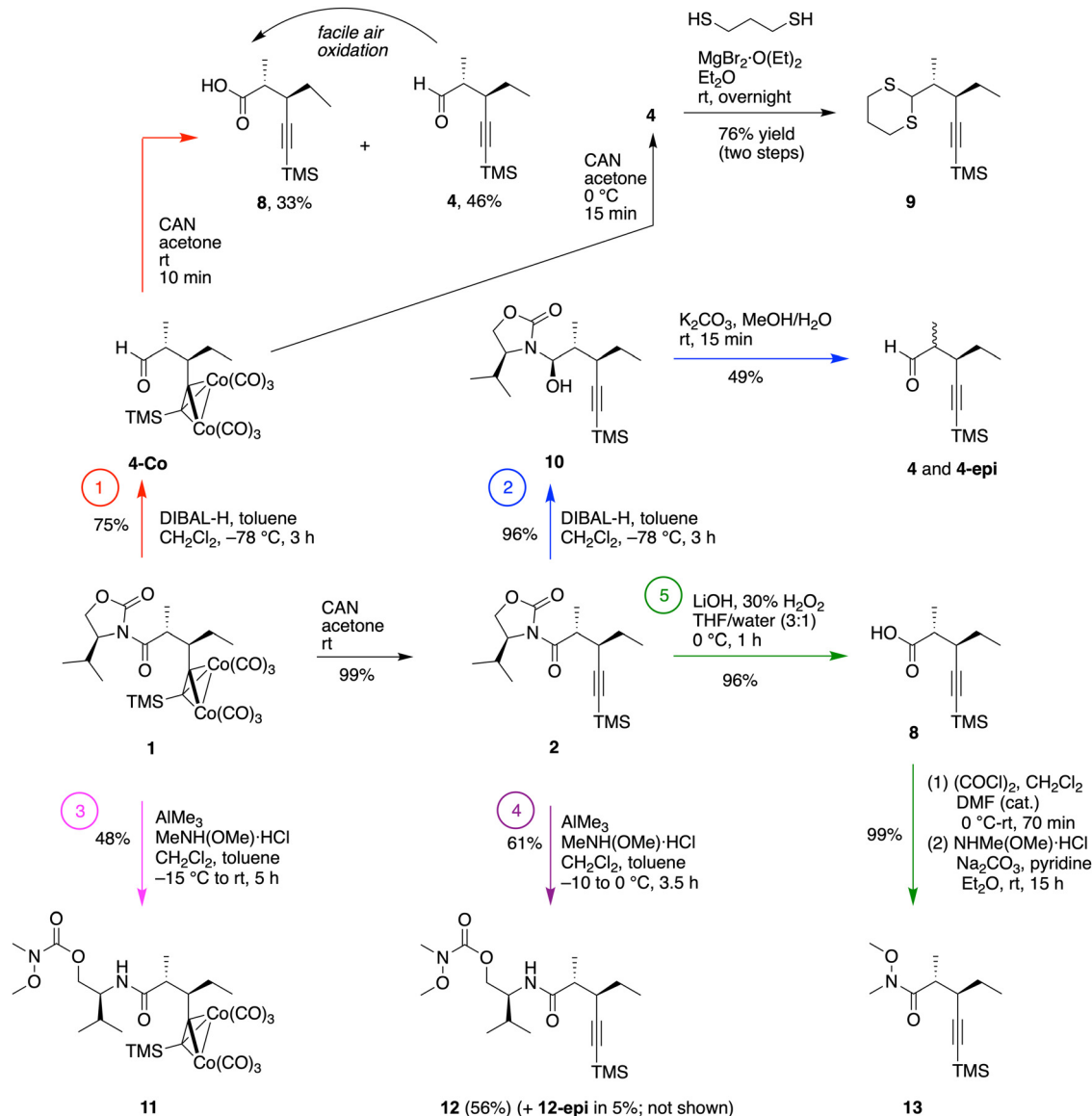
ones has been verified by single-crystal X-ray diffraction, indicating that one single diastereomer was formed in each case.[40] Treatment of **10** with K$_2$CO$_3$ in methanol/water (4 : 1 ratio)[39] promoted the rapid cleavage of the chiral auxiliary but also brought about epimerization at the C$_\alpha$ position as determined by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy, giving rise to a mixture of **4** and **4-epi** in 3 : 7 ratio (Scheme 5, upper middle). The proton at the C$_\alpha$ position (adjacent to the aldehyde) most likely underwent stereochemical scrambling *via* enol–keto tautomerization equilibrium in basic media. The ^{1}H NMR spectrum of the mixture of **4** and **4-epi** is compared with that of pure **4** in Fig. 1.

Given the oxidative and stereochemical lability of the chiral pentynal **4**, a route for the direct conversion of **1** or **2** to a chiral Weinreb pentynamide thereof was sought, given that the latter would be a versatile intermediate. Epimerization at the C$_\alpha$ position to an amide is regarded as far slower than that of an aldehyde.[41–43] Hence, routes 3–5 were pursued.

(3) Treatment of Schreiber-Nicholas adduct **1** to aluminum-mediated reductive cleavage in the presence of *N*,*O*-dimethylhydroxyamine hydrochloride[44–46] caused ring opening to the carbonyl group of the oxazolidinone unit to give undesired carbamate **11** (48%) (Scheme 5, lower left). Such endocyclic nucleophilic cleavage has been observed for hindered substrates[44,47] and explained by failure of the Lewis acid to coordinate to the exo carbonyl unit, which is crucial to trigger the exocyclic reduction pathway leading to the Weinreb pentynamide. On the other hand, the formation of such amides *via* endocyclic nucleophilic cleavage has rarely been reported.[48,49] The structure of **11** was confirmed by single-crystal X-ray diffraction (Fig. 2).

(4) Treatment of **2** to the same reaction conditions gave a mixture of two undesired but separable epimers, **12** (56%, a white solid) and **12-epi** (5%, an oil), as established by comparison of the ^{1}H and ^{13}C{^{1}H} NMR spectra as well as HRMS analyses (Scheme 5, lower middle). Examination of the main isomer (**12**) by single-crystal X-ray diffraction confirmed the nucleophilic ring-opening (Fig. 2). The results show that the *trans*-dialkyl motif was still sufficiently sterically hindered to suppress the exocyclic nucleophilic cleavage but not sufficiently bulky to impede the epimerization at the C$_\alpha$ site.

Scheme 5 Exploratory derivatization of Nicholas–Schreiber pentynamide **1**.

(5) In a less direct route, **2** was treated with LiOOH (generated *in situ* from LiOH and 30% H_2O_2)[47] at 0 °C to afford chiral pentynoic acid **8** in 96% yield (Scheme 5, lower right). The same reaction at room temperature[17] exclusively gave (2R,3R)-3-ethyl-2-methylpent-4-ynoic acid, a desilylated derivative of **8** (and isomer of **IVa**). Compound **8** was then treated[50,51] with oxalyl chloride followed by N,O-dimethylhydroxyamine hydrochloride under basic conditions to give desired **13** in 99% yield. The Weinreb pentynamide **13** can be used for sequential transformations without further purification.

In summary, the two approaches (1, 2) with DIBAL-H reduction gave the target pentynal **4** but typically with accompanying side products (carboxylic acid **8**, epimeric form **4-epi**) derived from oxidation and epimerization, respectively, during the reaction course or work-up procedures. Two direct routes (3, 4) to the Weinreb pentynamide were unsuccessful, whereas hydrolysis to form the carboxylic acid followed by

amidation (5) provided access in high yield to the Weinreb pentynamide **13**.

Diverse 1-substituted chiral hexynones

The chiral Weinreb pentynamide **13** served as the key scaffold for forming a family of chiral hexynones bearing a protected hydroxy group at the 1-position (Scheme 6). The transformation relied on access to one-carbon stannane synthons, which can undergo lithium–tin transmetalation[52,53] at low temperature (≤ -78 °C) to afford the corresponding *in situ* generated α-oxygenated organolithium nucleophiles. Compounds **Sn-Me**,[54] **Sn-MOM**,[55] **Sn-THP**,[56] **Sn-MEM**,[57] **Sn-Bn**[58] and **Sn-SEM**[59] were prepared according to literature procedures from tributyltin hydride *via* tributyl(iodomethyl)tin or tributyl(hydroxymethyl)tin[60] and characterized by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy; the syntheses are listed here for completeness. Chromatographic purification of compound[53] **Sn-(OMe)₂**
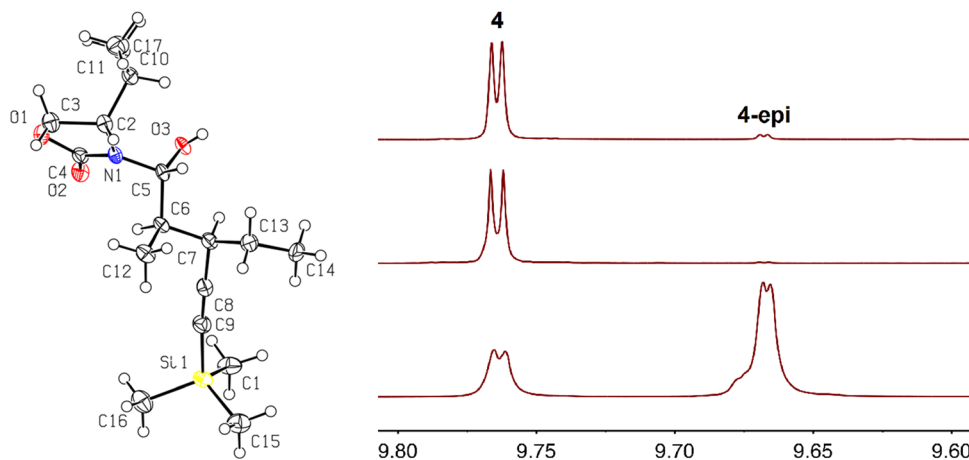
Fig. 1 ORTEP diagram with thermal ellipsoids drawn at the 50% probability level of **10** (left) and aldehydic region of the ¹H NMR spectrum of **4** (top right, prepared previously),[10] product from route 1 (middle right), and products prepared by route 2 (lower right).
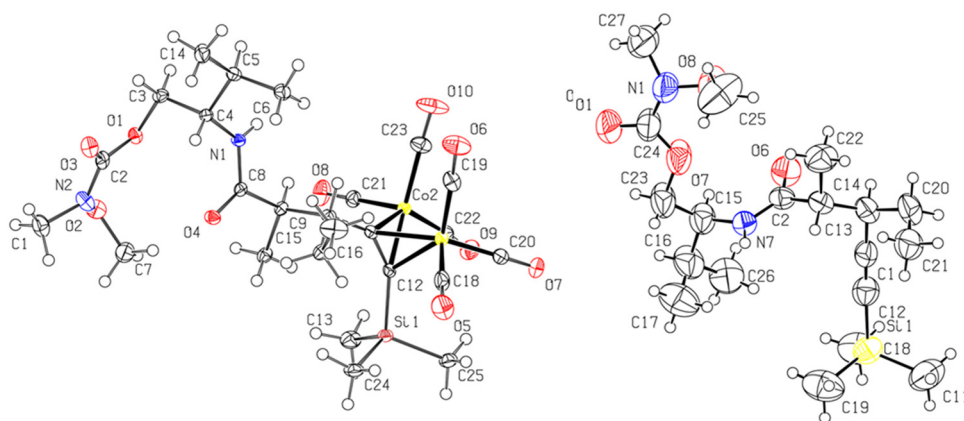

Fig. 2 ORTEP diagram of **11** (left) and **12** (right) with thermal ellipsoids drawn at the 50% probability level.
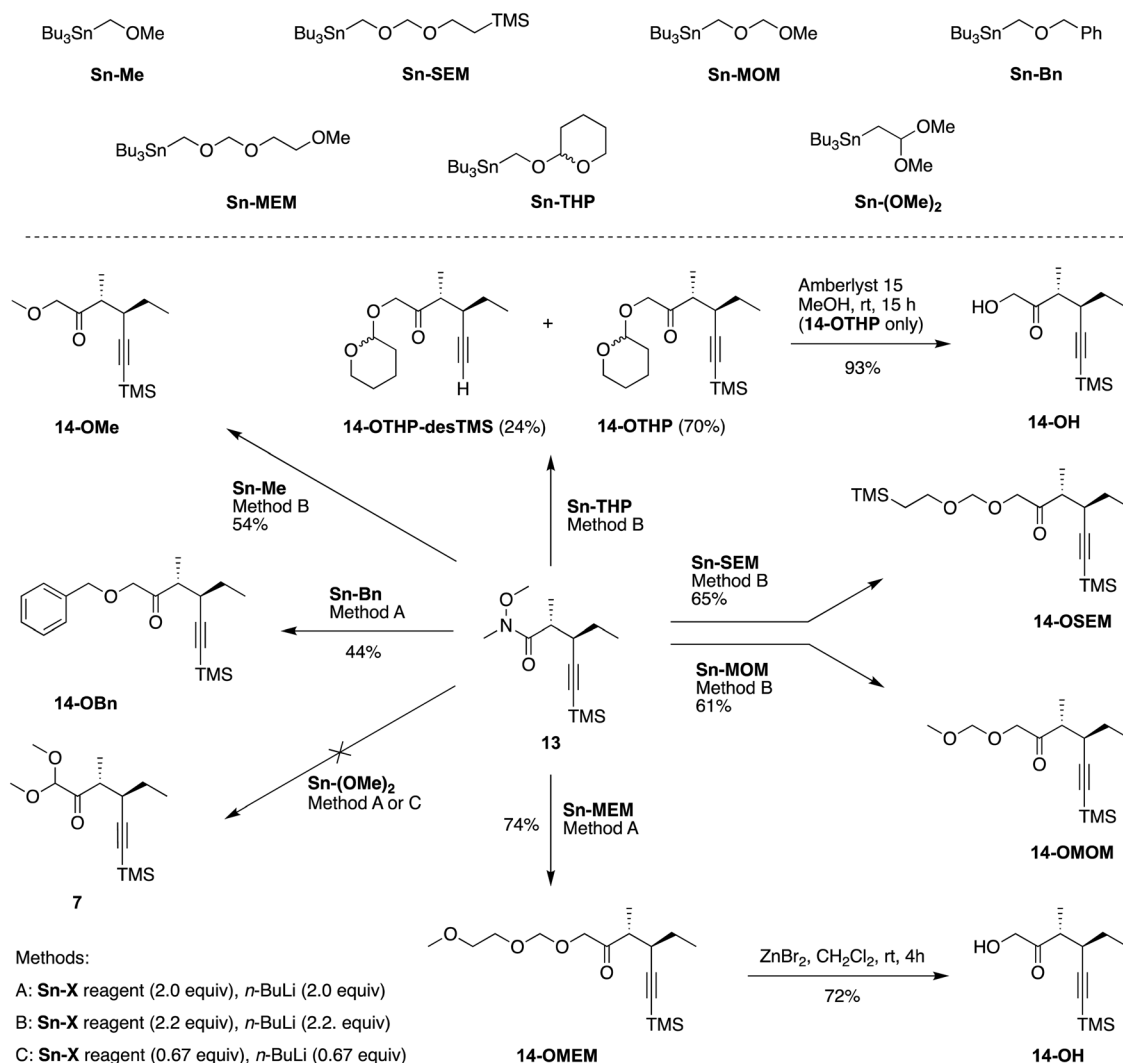
resulted in a significant loss of the product (although the ¹H and ¹³C{¹H} NMR spectra still matched the literature data[53]). To avoid the loss, **Sn-(OMe)₂** was used in crude form (quantitated by ¹H NMR analysis with use of mesitylene as an internal standard) for reactions.

The use of an organolithium reagent bearing an alkoxy group as nucleophile has been explored in reaction with Weinreb amides to afford compounds equipped with α-hydroxyketone motifs.[61,62] Thus, the organolithium reactant derived from **Sn-Me**, **Sn-SEM**, **Sn-MOM**, **Sn-Bn**, or **Sn-MEM** (by treatment of 2.0–2.2 equivalent of *n*-BuLi reagent with an equimolar amount of each (alkoxymethyl)stannane) underwent reaction[53] with **13** to give the corresponding adduct in similar yield, including **14-OMe** (54%), **14-OSEM** (65%), **14-OMOM** (61%), **14-OBn** (44%), or **14-OMEM** (74%). The reaction of **13** with the organolithium reactant derived from **Sn-THP** afforded two pairs of diastereomers. The first pair (isolated in 70% yield) consisted of two inseparable diastereomers of **14-OTHP** due to undefined stereochemistry of the anomeric carbon of the pyran ring. The second pair (24% yield) comprised two diastereomers of

14-OTHP-desTMS due to desilylation of the two parent epimers. The use of **Sn-(OMe)₂** in the attempted synthesis of **7** (bearing a dimethoxymethyl terminus) was not successful, as starting material **13** was recovered in 82% yield (method C) after chromatographic purification or 93% yield (method A) upon calculation from the crude reaction mixture with use of mesitylene as an internal standard. An alternative approach to convert **13** to **7** is described in the next section.

Altogether, six new chiral hexynones that differ in the nature of the protecting group for the 1-hydroxy substituent (Me, MOM, THP, MEM, Bn, or SEM) have been prepared. Deprotection attempts of selected compounds were also examined, showing that the transformation proceeded smoothly to afford the target compound **14-OH** in yields of 72% (from **14-OMEM** by treatment with ZnBr₂) or 93% (from **14-OTHP** by treatment with Amberlyst 15). The integrity of the stereochemical features of the *trans*-dialkyl moiety remained intact under the deprotection approaches examined. The chiral hexynones with Me, MOM, THP, MEM, Bn, SEM or no protection for the 1-hydroxy group comprise a collection of precursors to dihydrodipyrrins for

Scheme 6 Diversification to form chiral 4-hexyn-2-ones (lower panel) with use of tributyltin-one-carbon synthons (top panel).

methodology development in the preparation of (bacterio)-chlorophylls.

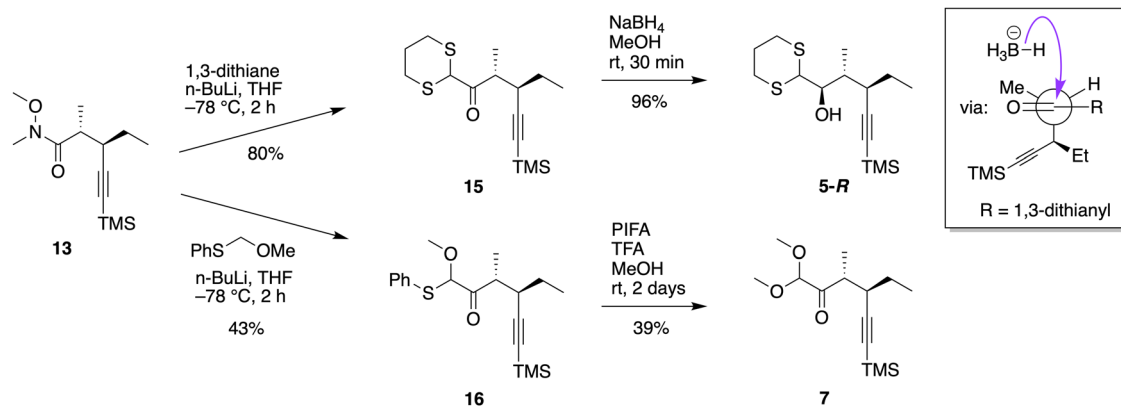## Improved preparation of intermediates on the path to IX, a pre-B compound

The failure to convert **13** to **7** *via* stannane **Sn-(OMe)₂** prompted studies using the chiral Weinreb pentynamide **13** as a key scaffold to gain improved access to intermediates on the path to hexynone **IX**. Thus, one-carbon synthons for nucleophilic addition to the Weinreb amide **13** were explored, with the proviso that the added moieties would be amenable to subsequent transacetalization (Scheme 7). The anticipated advantages of derivatization of pentynamide **13** *versus* pentynal **4** included sidestepping the risk of epimerization as well as avoidance of any oxidation steps following the nucleophilic addition.

First, pentynamide **13** was treated with lithiated 1,3-dithiane at −78 °C[63] for 2 h to afford acyldithiane **15** in 80% yield. Treatment of **15** with PIFA in anhydrous methanol[10] gave none of the desired product. Such failures of transacetalization of the dithiane group of analogues of **15** are known.[63–65] Recourse was

achieved by reduction of **15** with NaBH₄ to obtain **5-R** in nearly quantitative yield. The newly formed stereocenter (carbinol) was assigned by comparing the ¹H NMR spectrum of **5-R** with the reported spectrum of the same compound.[10] Moreover, the highly stereoselective reduction of acyldithiane **15** can be explained *via* a modified Felkin–Anh model (see inset in Scheme 7).[66] In summary, use of 1,3-dithiane as a one-carbon synthon provided access to **IX** in a slightly better overall yield (73% from **2** here *versus* 67% from **2** previously[10]), albeit *via* a lengthier route, but with the advantage of limited handling of the epimerization-susceptible pentynal **4**.

Second, pentynamide **13** was treated with lithiated methoxy-methyl(phenyl)sulfane at −78 °C[64] to give **16** as a mixture of diastereomers (1 : 0.3 ratio) in 43% yield. Treatment of **16** with CuCl₂/CuO[64] or HgCl₂/HgO[67] in refluxing anhydrous methanol gave a complex mixture. The oxothioacetal **16** upon treatment with 3 equivalents of PIFA in anhydrous methanol gave only ∼50% conversion (on the basis of ¹H NMR analysis), and the mixture of **16** and **7** (1 : 1 ratio) was inseparable by conventional silica gel chromatography. Ultimately, the synergistic effect of

Scheme 7 Refined synthesis of chiral hexynone **IX** (pre-B) precursors.

PIFA and TFA in anhydrous methanol gave conversion of **16** to **7** but with isolation of the latter in only 39% yield. Thus, both compounds **5-R** and **7** can be transformed to chiral hexynone **IX** (the pre-B compound) *via* known routes (Scheme 4).[10]

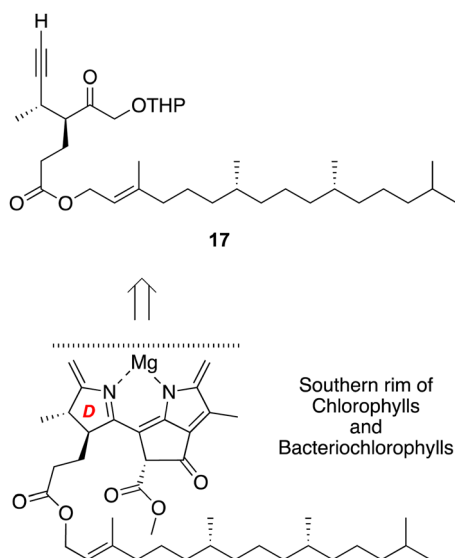### Phytyl-containing ring D precursor

Chlorophyll *a* and bacteriochlorophyll *a* share a common structure of the Southern rim as is shown in Chart 1. Across the photosynthetic tetrapyrroles, a few macrocycles contain a 17-acrylic acid moiety rather than a 17-propionic acid group, and there are variants particularly among bacteriochlorophylls in the nature of the hydrocarbon chain that forms the ester of the propionic acid unit, but otherwise the southern rims are identical. The rim also is similar if not identical across many catabolites of chlorophylls, the phyllobilins.[68–72] Both photosynthetic hydroporphyrins[73] and phyllobilins[74] are largely unexplored with regards to synthesis. A retrosynthesis corresponding to ring D of native photosynthetic hydroporphyrins

Scheme 8 Ring D building block equipped with a phytyl tail.

(and many phyllobilins, although the ring labeling is different) in terms of the chiral hexynone **17** is shown in Scheme 8.

A key objective is to be able to prepare photosynthetic tetrapyrroles in sufficient quantity (*e.g.*, 10 mg each) for studies in the photosciences. As the syntheses are expected to have a modular nature, access to ample quantities of core building blocks is desired. The synthesis of **17** proceeds through intermediates **18–29**. The preparation of compounds **18–23** has been reported,[26] but was carried out here at larger scale, in streamlined fashion, or in higher yield. The improved synthesis along the series **18–23** is reported first, followed by extension of **23** to form the phytyl target **17**.

Treatment of penta-1,5-diol *via* a four-step synthesis without purification of crude intermediates (method A)[26] gave the activated ester **18** in 64% yield. Alternatively, **18** could be approached in 26% yield through a two-step route with use of (diacetoxyiodo)benzene (DIB) and *N*-hydroxysuccinimide (NHS) as an oxidant and an activating reagent,[75] respectively, after monoprotection of pentan-1,5-diol (method B). Compound **18** was obtained as a white solid upon recrystallization in absolute ethanol (method A) but a colorless oil upon column chromatography (method B and previous route[26]). The conversion of (trimethylsilyl)acetylene to Nicholas substrate **19** (92% yield) was accomplished in one-flask fashion (*versus* the previous two-flask approach[17]) followed by short flash column chromatographic purification (Scheme 9). Analogous reactions from methyl 3-trimethylsilyl propargyl ether,[30,31] 3-(trimethylsilyl)propynal,[9] or 4-(trimethylsilyl)but-3-yn-2-ol (two-step synthesis)[26] also afforded the same compound **19** (67–85% yield) but in smaller scale. In this manner, **18** and **19** – two key building blocks for ring D synthesis – were obtained in quantities of 75.34 g (166 mmol) and 73.59 g (174 mmol), respectively.
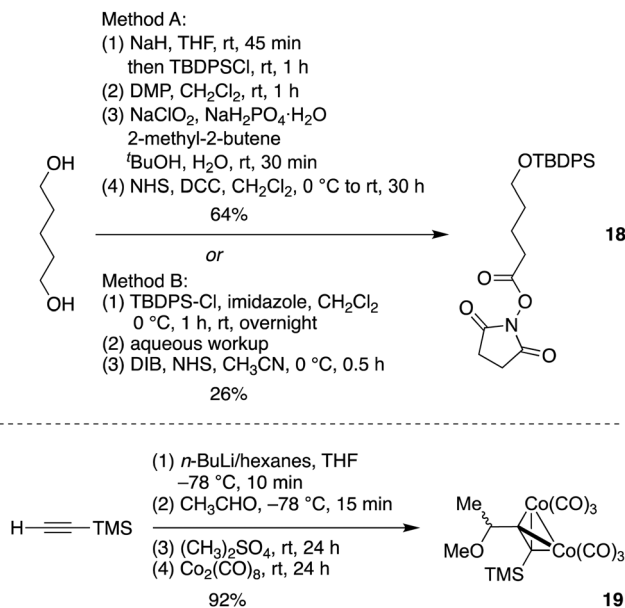
The formation of the chiral hexynone unit of phytyl target **17** was achieved *via* the general route described above, which entails the Schreiber-modified Nicholas reaction followed by path 5 in Scheme 5. The reaction scheme beginning with (*R*)-3-isopropyloxazolidinone *via* intermediates **20–22** is known[26] but was refined here. Thus, reaction of (*R*)-3-isopropyloxazolidinone with *n*-butyl lithium followed by **18** gave **20** in 88% yield (Scheme 10). Subsequent reaction with dibutylboron

Scheme 9 Streamlined synthesis of precursors.

triflate in the presence of N,N-diisopropylethylamine (DIPEA) followed by Nicholas substrate **19** gave the Schreiber-Nicholas product **21** containing two contiguous stereocenters. The higher yield here (90% *versus* 68% previously[26]) is attributed to the use of less dibutylboron triflate (1.5 *versus* 2 equiv.) and shorter reaction time (85 *versus* 120 minutes). Decomplexation upon treatment with CAN quantitatively gave **22**. Previous hydrolysis of **22** with LiOOH at room temperature gave the desilylated product **IVb** as the dominant product (74% yield) along with that having an intact TMS group (**23**, 13% yield).[26] Here, the same hydrolysis at 0 °C afforded a reversal in the ratio, giving **IVb** and **23** in 17% and 75%, respectively. A single-crystal X-ray structure of the xylyl amide derivative of **IVb** was determined to establish the stereochemistry.[26]

Compound **23** was transformed into the corresponding Weinreb pentynamide **24** in 81% yield by treatment[51] with oxalyl chloride followed by N,O-dimethylhydroxyamine hydrochloride (Scheme 10). The nucleophilic addition of the organolithium reagent[53] derived from **Sn-THP** to Weinreb pentynamide **24** gave THP-protected hexynone **26** in 64% yield. The same chemistry was carried out on the desilylated compound **IVb** to give the Weinreb pentynamide **25** in 83% yield. The reaction of **25** with excess **Sn-THP** and n-BuLi reagents (2.5 to 4.0 equiv.) only afforded the adduct **27** in yields ranging from 14% to 34%, respectively, with **25** recovered in 51–62% yield. Attempts to use even larger amounts (>4 equiv.) of the organotin and n-BuLi reagents required laborious workup to purify the product from unreacted starting material and a large quantity of impurities.

Treatment of **26** with TBAF at 0 °C followed by DIB-TEMPO-mediated oxidation gave a mixture of the aldehyde **28** and the carboxylic acid **29** in 25% and 50% yield, respectively. The aldehyde **28** in its entirety was subjected to Pinnick oxidation[76] to quantitatively afford the carboxylic acid **29**. The final step for installation of the native phytyl group was achieved by Steglich

esterification,[77] mediated by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2. Thus, reaction of chiral hexynone **29** and native phytol gave the target **17** as a light-yellow oil in 61% yield (1.43 g). Native phytol was employed, hence the product is semisynthetic. The product **17** contains six stereocenters (two adjacent centers of chirality in the hexynone moiety; two centers of chirality and the E alkene in the phytol unit; and the chiral THP unit) and is a mixture of two diastereomers given the configuration of the THP protecting group.
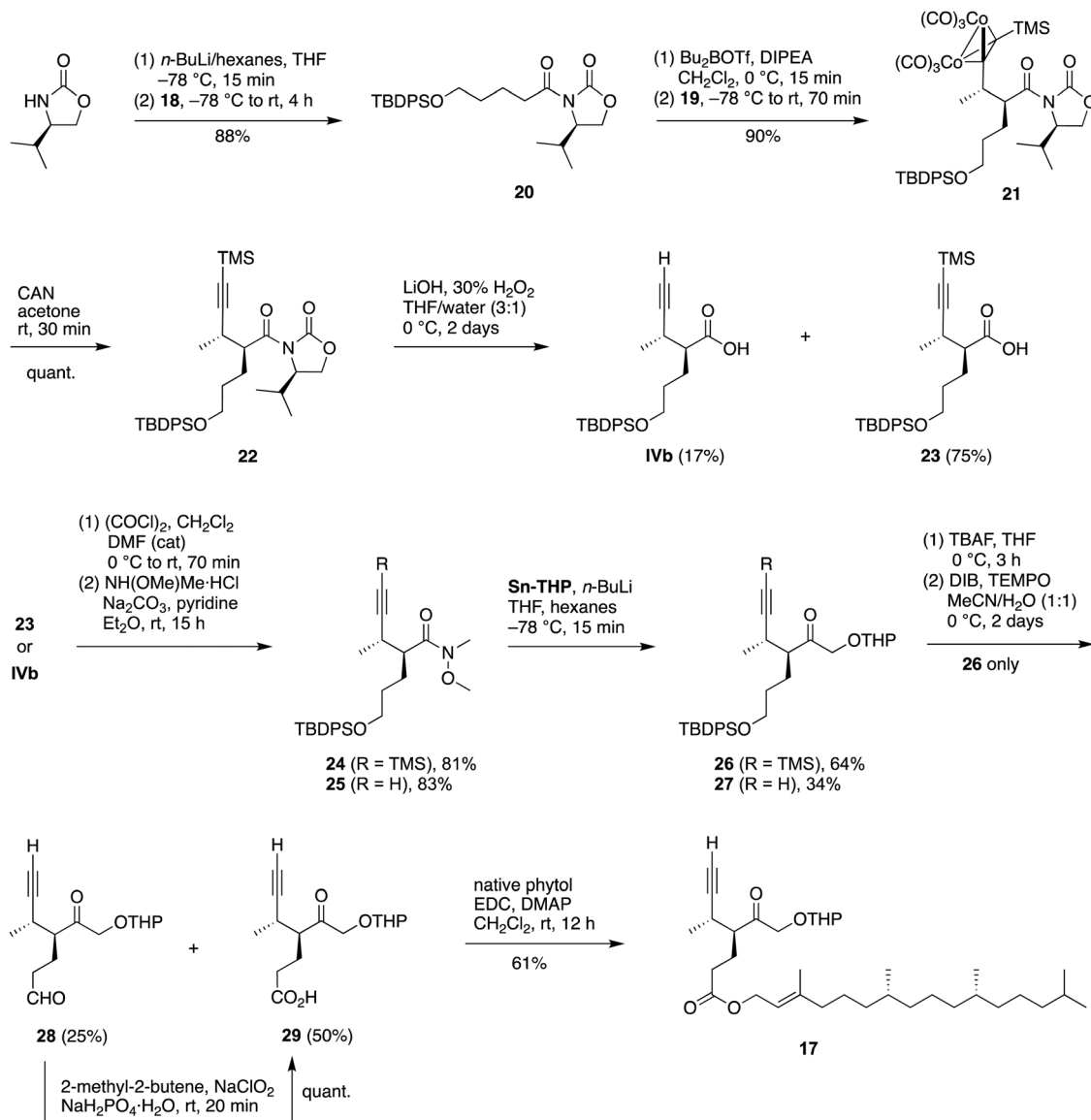
Outlook

A planned total synthesis of photosynthetic tetrapyrroles installs the requisite stereocenters in the pyrroline rings at a very early stage of the synthesis. An advantage of doing so is the ability to rely on established methodology of asymmetric chemistry; a challenge to doing so is the requirement to carry the stereocenters with fidelity throughout the course of the synthesis. In all of the chiral hexynones and the prior pentynoic acid derivatives, each stereocenter is adjacent to an electron-withdrawing group (ethyne or carbonyl) and hence is vulnerable to epimerization.[41–43] The synthetic approaches for installation of the one-carbon handles must be done in a manner compatible with the established stereochemical configuration at the two sites.

The Schreiber-modified Nicholas reaction is a time-honored method to install two contiguous stereochemical centers in an alkynyl–amide. Direct reduction of the Schreiber-Nicholas adduct **1** with DIBAL-H and subsequent removal of the hexacarbonyldicobalt protecting group gave pentynal **4**, which proved to be quite labile (Scheme 5). Hydrolysis of the amide linking the oxazolidinone chiral auxiliary in **2** released the chiral pentynoic acid (**8**), which was converted to the chiral Weinreb pentynamide **13** (Scheme 5). The availability of the chiral Weinreb pentynamide **13** opened access to late-stage derivatization with use of a handful of (alkoxymethyl)stannane reagents thereby creating a family of 1-substituted chiral hexynones (Scheme 6). The compound of perhaps greatest immediate interest, **7**, the TMS-protected derivative of **IX** (a pre-B compound), was not accessible *via* the (1,1-dimethoxymethyl)stannane reagent **Sn-(OMe)₂** (Scheme 6). Instead, the Weinreb pentynamide (**13**) was reacted with lithiated 1,3-dithiane or methoxymethyl-(phenyl)sulfane to install the 1-carbon of the nascent chiral hex-5-yn-2-one; the former following borohydride treatment afforded dithianyl–alcohol **5-R** whereas the latter following PIFA-mediated transacetalization with methanol afforded **7** (Scheme 7). Both **5-R** and **7** can funnel into the established route (Scheme 4) to give **IX**.

The diverse collection of 1-substituted chiral hexynones prepared herein may be of value in development of methodology in the (bacterio)chlorophyll domain. While the immediate target is bacteriochlorophyll a, a broader goal is to be able to create a family of native photosynthetic macrocycles as well as analogues and stereoisomers thereof. Both objectives impose requirements of scale. Here, selected chiral hexynones (**17**, **26**) have been prepared in gram quantities (2.5 mmol, 12 mmol) for use in the total syntheses, which are 250 or 1200 times larger

Scheme 10 Synthesis of the chiral phytyl-containing ring D precursor.

than the quantity of target hydroporphyrin. Known and new routes have been implemented in refined and/or streamlined fashion to enable synthesis at such scale of chiral hexynones, which may be of use in a variety of syntheses aimed at preparing photosynthetic hydroporphyrins.

Experimental section

General information

All chemicals from commercial sources were used as received. Silica for column chromatography was 230–400 mesh (60 Å). THF for use in inert-atmosphere reactions was freshly distilled from sodium/benzophenone ketyl. Other solvents were reagent grade and used as received unless noted otherwise. Phytol was obtained from AmBeed, Inc.

Low-temperature reactions

Reaction at temperatures lower than ambient were obtained with ice water (0 °C); ice water/NaCl mixtures (−15 or −10 °C); dry ice/NaCl/water (−20 °C); dry ice/acetone or dry ice/diethyl ether (−78 °C). The dry ice/diethyl ether bath is reported to afford a temperature of −100 °C[78] but in our hands was found to be −78 °C by use of a calibrated digital thermometer. The stated temperatures are for the bath, not the contents of a reaction flask immersed therein.

Known compounds

Known compounds Sn-(OMe)$_2$,[53] Sn-Me,[54] Sn-MOM,[55] Sn-THP,[56] Sn-MEM,[57] Sn-Bn,[58] and Sn-SEM[59] were prepared as described in the literature. Known compounds 18–23 and IV-b were prepared herein in streamlined syntheses and/or in larger scales than reported previously.[26] Known compounds

4,[10] 5-R,[10] and 7[10] were prepared by new routes as described herein.

Synthesis and characterization

(2R,3R)-3-Ethyl-2-methyl-5-(trimethylsilyl)pent-4-ynal, Hexacarbonyldicobalt complex (4-Co). Following a literature procedure[36] with modifications, a solution of **1** (1.83 g, 3.00 mmol) in CH_2Cl_2 (60 mL) at −78 °C under argon was treated dropwise over 5 min with DIBAL-H (1.2 M solution in toluene, 6.0 mL, 7.2 mmol). The reaction mixture was stirred at −78 °C for 3 h followed by treatment with saturated aqueous NH_4Cl solution (30 mL) under vigorous stirring. The mixture was allowed to warm to room temperature, at which point aqueous tartaric acid (0.5 M, 50 mL) was added following by stirring for 15 min and extraction with CH_2Cl_2 (3 × 30 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (5:1)] to afford a dark-brown solid (1.08 g, 75%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.34 (s, 9H), 0.92 (t, J = 7.5 Hz, 3H), 1.23 (d, J = 7.2 Hz, 3H), 1.68 (p, J = 7.4 Hz, 2H), 2.64 (q, J = 7.3 Hz, 1H), 3.52 (t, J = 7.2 Hz, 1H), 9.80 (s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 1.3, 8.5, 13.6, 27.7, 44.9, 53.2, 80.4, 116.9, 200.4, 203.4; HRMS (ESI-FTMS) m/z: $[M + H]^+$ calcd for $C_{17}H_{22}Co_2O_7Si$ 482.9715; found, 482.9719.

Formation of 4 and 8 by decomplexation of 4-Co

A solution of **4-Co** (1.07 g, 2.20 mmol) in acetone (50 mL) at room temperature was treated in portions with CAN (5.00 g in total). Then, the reaction mixture was stirred at room temperature for 10 min, after which water (50 mL) was added and the resulting mixture was concentrated. The residue was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extract was dried (Na_2SO_4) and concentrated to afford a light-yellow oil (366.7 mg) comprised of two components, which were determined to be the aldehyde **4** and the carboxylic acid **8** (3:2 ratio determined by ^{1}H NMR spectroscopy) in isolated yield of 46% and 33%, respectively. The mixture was chromatographed [silica, hexanes/ethyl acetate (20:1) then (1:1)] to afford two fractions (each a colorless oil). The first fraction (92.8 mg) proved to be aldehyde **4** (one spot observed on TLC) but underwent degradation to **8** (upon contact with air in the fume hood) prior to authentication by NMR spectroscopy. The second fraction (208.2 mg) was determined to be **8**. The following data are for the crude mixture (366.7 mg) prior to chromatography: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 9H from **8**), 0.15 (s, 9H from **4**), 1.01–1.05 (m, 3H for each component), 1.17 (d, J = 7.1 Hz, 3H from **4**), 1.23 (d, J = 6.6 Hz, 3H from **8**), 1.42–1.54 (m, 2H for each component), 2.39–2.44 (m, 1H from **4**), 2.55 (dt, J = 8.8, 5.7 Hz, 1H from **4**), 2.63–2.71 (m, 2H from **8**), 9.77 (d, J = 2.3 Hz, 1H from **4**); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 0.2, 11.98, 12.01, 12.1, 13.5, 24.1, 25.6, 36.2, 37.3, 43.4, 49.2, 87.5, 88.5, 106.8, 107.5, 204.7.

(1R,2R,3R)-1-(1,3-Dithian-2-yl)-3-ethyl-2-methyl-5-(trimethylsilyl)pent-4-yn-1-ol (5-R). A solution of **15** (33.3 mg, 0.106 mmol) in 1 mL of anhydrous methanol was treated with NaBH$_4$ (4.5 mg, 0.12 mmol) at 0 °C under argon for 30 min. The

reaction mixture was treated with saturated aqueous NH_4Cl solution (5 mL), and the resulting mixture was extracted with CH_2Cl_2 (4 × 3 mL). The combined organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure to obtain a white solid (32.2 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 9H), 1.03–1.00 (m, 6H), 1.38–1.32 (m, 1H), 1.58–1.51 (m, 1H), 2.01–1.87 (m, 1H), 2.17–2.02 (m, 1H), 2.50 (d, J = 4.8 Hz, 1H), 2.68–2.64 (m, 1H), 2.81–2.76 (m, 1H), 3.01–2.86 (m, 3H), 3.82 (dt, J = 7.8, 4.5 Hz, 1H), 4.30 (d, J = 4.1 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 0.4, 12.3, 13.9, 23.5, 26.0, 28.7, 29.7, 36.4, 39.7, 51.4, 75.8, 87.1, 110.3; HRMS (ESI-FTMS) m/z: $[M + H]^+$ calcd for $C_{15}H_{29}OS_2Si$ 317.1424; found, 317.1423.

(3R,4R)-4-Ethyl-1,1-dimethoxy-3-methyl-6-(trimethylsilyl)-hex-5-yn-2-one (7). A solution of **16** (48.0 mg, 0.138 mmol) in anhydrous methanol at room temperature was treated with trifluoroacetic acid (32 μL, 0.42 mmol) followed by PIFA (88.8 mg, 0.206 mmol). After 1 h, an additional quantity of PIFA (88.8 mg, 0.206 mmol) was added. After a further 1 h, a third quantity of PIFA (17.8 mg, 0.04 mmol) was added. The resulting mixture was stirred overnight at room temperature, and then treated with trifluoroacetic acid (32 μL, 0.42 mmol) and PIFA (88.8 mg, 0.206 mmol). The reaction mixture was allowed to stir for 24 h at room temperature, and then saturated aqueous NaHCO$_3$ solution (5 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (10:1)] to obtain a viscous oil (14.7 mg, 39%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.01 (t, J = 7.3 Hz, 3H), 1.09 (d, J = 7.0 Hz, 3H), 1.39–1.30 (m, 1H), 1.59–1.51 (m, 1H), 2.64–2.60 (m, 1H), 3.13–3.06 (m, 1H), 3.40 (s, 3H), 3.41 (s, 3H), 4.69 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 0.3, 11.5, 13.6, 23.9, 36.2, 45.0, 54.5, 54.7, 86.9, 103.6, 108.5, 207.1; HRMS (ESI-FTMS) m/z: $[M + H]^+$ calcd for $C_{14}H_{27}O_3Si$ 271.1724; found, 271.1722.

Two-step synthesis, *via* 4, of 1-(1,3-Dithian-2-yl)-(1R,2R)-2-ethyl-1-methyl-4-(trimethylsilyl)but-3-yne (9). A solution of **4-Co** (5.40 g, 11.1 mmol) in acetone (200 mL) at 0 °C under argon was treated in portions with CAN (in total 46.0 g, 83.9 mmol) over the course of 5 min. The resulting mixture was then stirred for 15 min at the same condition, and then treated with water (150 mL). The mixture was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic extract was dried (Na_2SO_4) and then concentrated under reduced pressure at low temperature (0–5 °C) to obtain crude pentynal **4** as a colorless oil.

In a separate flask, a suspension of MgBr$_2$·OEt$_2$ (3.46 g, 13.4 mmol) in anhydrous diethyl ether (31 mL) at room temperature under argon was treated dropwise with propane-1,3-dithiol (1.30 mL, 12.8 mmol) over the course of 15 min.[37] Then, the mixture of MgBr$_2$·OEt$_2$ (3.46 g, 13.4 mmol) and propane-1,3-dithiol was treated with a solution of the crude pentynal **4** (assumed 11.1 mmol) in anhydrous diethyl ether (13 mL). The reaction mixture was allowed to stir overnight at room temperature under argon, and then treated with water (150 mL). The mixture was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl

acetate (20:1)] to obtain a colorless oil (1.81 g, 76%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.17 (s, 9H), 1.01 (t, J = 7.4 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H), 1.36–1.30 (m, 1H), 1.63–1.57 (m, 1H), 1.96–1.81 (m, 2H), 2.14–2.09 (m, 1H), 2.54 (dt, J = 9.2 and 4.6 Hz, 1H), 2.99–2.81 (m, 4H), 4.57 (d, J = 4.6 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 0.4, 11.5, 14.0, 23.9, 26.6, 31.0, 31.7, 38.0, 41.8, 54.6, 87.2, 108.9; HRMS (ESI-FTMS) m/z: [M + H]$^+$ calcd for C$_{14}$H$_{27}$S$_2$Si 287.1318; found, 287.1318.

(4S)-3-((2R,3R)-3-Ethyl-1-hydroxy-2-methyl-5-(trimethylsilyl)-pent-4-yn-1-yl)-4-isopropyloxazolidin-2-one (10). Following a literature procedure with modifications,[36] a solution of **2** (970.5 mg, 3.00 mmol) in CH$_2$Cl$_2$ (60 mL) under argon at −78 °C was treated dropwise over 5 min with DIBAL-H (1.2 M solution in toluene, 6.0 mL, 7.2 mmol). The reaction mixture was stirred at −78 °C for 3 h, then treated with saturated aqueous NH$_4$Cl solution (30 mL) under vigorous stirring. The mixture was allowed to warm to room temperature, at which point aqueous tartaric acid (0.5 M, 50 mL) was added following by stirring for 15 min and subsequent extraction with CH$_2$Cl$_2$ (3 × 30 mL). The combined organic extract was dried (Na$_2$SO$_4$) and concentrated to give a white solid (939.4 mg, 96%): m.p. 118–120 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.15 (s, 9H), 0.93 (d, J = 7.0 Hz, 3H), 0.98–1.04 (m, 9H), 1.42–1.57 (m, 2H), 2.14 (ddq, J = 10.3, 6.9, and 3.5 Hz, 1H), 2.39–2.46 (m, 1H), 2.57 (dt, J = 10.4 and 4.4 Hz, 1H), 3.75 (dt, J = 8.6 and 3.4 Hz, 1H), 4.05 (d, J = 10.7 Hz, 1H), 4.15 (dd, J = 9.0, 3.3 Hz, 1H), 4.26 (t, J = 8.8 Hz, 1H), 4.70 (dd, J = 10.7 and 9.0 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 0.3, 12.5, 13.3, 14.8, 18.1, 23.3, 29.4, 37.3, 42.0, 61.5, 64.1, 82.0, 87.3, 109.0, 158.5; HRMS (ESI-FTMS) m/z: [M + H]$^+$ calcd for C$_{17}$H$_{32}$NO$_3$Si 326.2146; found, 326.2151. The title compound upon slow evaporation from acetonitrile afforded a crystalline sample that was then examined by single-crystal X-ray diffraction (Bruker D8 Venture instrument using Mo Kα-radiation). The structure was determined and refined using Olex2 and SHELXT programs.

Formation of 4 and 4-epi by hydrolysis of 10

Following a literature procedure,[40] a solution of **10** (931.0 mg, 2.86 mmol) in methanol/water [4:1 (v/v) ratio, 200 mL] was treated with K$_2$CO$_3$ (552.8 mg, 4.00 mmol). The reaction mixture was stirred at room temperature for 15 min followed by concentration and extraction with CH$_2$Cl$_2$ (3 × 30 mL). The combined organic extract was purified through a silica pad [hexanes/ethyl acetate (20:1)] to afford a colorless oil (275.9 mg, 49%) comprised of two epimers of (**4 and 4-epi**) in 3 : 7 molar ratio as determined by ^{1}H NMR spectroscopy: ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.13 (s, 9H, major epimer), 0.14 (s, 9H, minor epimer), 0.99–1.05 (m, 3H for each epimer), 1.16–1.18 (m, 3H for each epimer), 1.45–1.54 (m, 2H for each epimer), 2.37–2.45 (m, 1H for each epimer), 2.55 (dt, J = 8.6 and 5.6 Hz, 1H, minor epimer), 2.76 (q, J = 6.9 Hz, 1H, major epimer), 9.67 (d, J = 1.7 Hz, 1H, major epimer), 9.76 (d, J = 2.3 Hz, 1H, minor epimer); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 0.2, 10.4, 11.97, 12.00, 12.1, 25.6, 26.0, 35.2, 36.2, 49.16, 49.18, 88.3, 88.4, 106.3, 106.8, 204.1, 204.7.

(2R,3R)-3-Ethyl-N-((S)-1-hydroxy-3-methylbutan-2-yl)-N-(meth-oxy(methyl)carbamoyl)-2-methyl-5-(trimethylsilyl)pent-4-ynamide hexacarbonyldicobalt complex (11). Following a literature procedure,[46] a solution of N,O-dimethylhydroxyamine hydrochloride (195 mg, 2.00 mmol) in CH$_2$Cl$_2$ (8 mL) at 0 °C was treated dropwise with trimethylaluminum (2 M in toluene, 1.00 mL, 2.0 mmol). The resulting mixture was cooled at −15 °C, treated with a solution of compound **1** (609 mg, 1.00 mmol) in CH$_2$Cl$_2$ (3.5 mL), allowed to warm to room temperature, and stirred at room temperature for 5 h. Then, the reaction mixture was treated with 1 M Rochelle salt solution (15 mL). The mixture was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic extract was dried (Na$_2$SO$_4$), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (5:1)] to afford a dark-red solid (319 mg, 48%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.20 (s, 9H), 0.82–0.90 (m, 9H), 1.09 (d, J = 7.1 Hz, 3H), 1.33–1.79 (m, 3H), 2.50 (q, J = 7.3 Hz, 1H), 3.00 (s, 3H), 3.27–3.29 (m, 1H), 3.52 (d, J = 13.6 Hz, 3H), 3.92–4.03 (m, 2H), 4.14–4.21 (m, 1H), 5.67 (t, J = 8.6 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 1.3, 10.7, 13.7, 18.7, 19.3, 27.0, 29.8, 35.6, 47.1, 47.8, 54.0, 61.8, 65.9, 80.6, 117.8, 157.4, 174.3, 200.6; HRMS (ESI-FTMS) m/z: [M + H]$^+$ calcd for C$_{25}$H$_{37}$Co$_2$N$_2$O$_{10}$Si 671.0876; found, 671.0872. Compound **11** upon slow evaporation from acetonitrile afforded a crystalline sample that was then examined by single-crystal X-ray diffraction (Bruker D8 Venture instrument using Mo Kα-radiation). The structure was determined and refined using Olex2 and SHELXT programs.

(2R,3R)-3-Ethyl-N-((S)-1-hydroxy-3-methylbutan-2-yl)-N-(methoxy-(methyl)carbamoyl)-2-methyl-5-(trimethylsilyl)pent-4-ynamide and epimer (12 and 12-epi). Following a literature procedure,[45] a solution of N,O-dimethylhydroxyamine hydrochloride (658 mg, 6.75 mmol) in CH$_2$Cl$_2$ (9.2 mL) at −10 °C was treated dropwise with trimethylaluminum (2 M in toluene, 3.38 mL, 6.8 mmol). The resulting mixture was allowed to warm to 0 °C and stirred at the same temperature for 15 min (until gas evolution ceased). The mixture was then cooled to −10 °C again, treated with a solution of **2** (728 mg, 2.25 mmol) in CH$_2$Cl$_2$ (9.2 mL), and stirred for 1 h at −10 °C, 2 h at 0 °C, and 0.5 h at room temperature. The resulting mixture was poured into an ice-cold mixture of aqueous 0.5 M HCl (50 mL) and CH$_2$Cl$_2$ (25 mL), followed by vigorous stirring for 5 min and extraction with CH$_2$Cl$_2$ (3 × 25 mL). The combined organic extract was washed with pH 7 buffer solution (0.1 M, potassium phosphate), dried (Na$_2$SO$_4$), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (2:1)] to afford two products.

12-epi (48 mg, colorless oil): ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.13 (s, 9H), 0.93–1.02 (m, 9H), 1.19 (d, J = 6.6 Hz, 3H), 1.36–1.51 (m, 2H), 1.86 (hept, J = 6.8 Hz, 1H), 2.62–2.68 (m, 2H), 3.08 (s, 3H), 3.66 (s, 3H), 3.85 (ddd, J = 10.5, 8.4, and 5.3 Hz, 1H), 4.08 (dd, J = 11.4 and 4.2 Hz, 1H), 4.25 (dd, J = 11.4 and 6.1 Hz, 1H), 5.82 (d, J = 9.5 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 0.3, 12.0, 13.7, 18.7, 19.5, 24.1, 29.9, 35.7, 37.4, 43.6, 54.2, 61.5, 64.8, 87.1, 107.8, 160.2, 174.6; HRMS (ESI-FTMS) m/z: [M + H]$^+$ calcd for C$_{19}$H$_{37}$N$_2$O$_4$Si 385.2517; found, 385.2516.

12 (482 mg, white solid): m.p. 44–46 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.13 (s, 9H), 0.94–1.00 (m, 9H), 1.20 (d, J = 7.1 Hz, 3H),

1.42 (ddt, J = 17.0, 13.2, and 7.3 Hz, 1H), 1.53 (dtd, J = 14.7, 7.4, and 4.8 Hz, 1H), 1.82 (hept, J = 6.7 Hz, 1H), 2.39 (p, J = 7.0 Hz, 1H), 2.53 (ddd, J = 9.7, 6.8, and 4.7 Hz, 1H), 3.11 (s, 3H), 3.65 (s, 3H), 4.05–4.12 (m, 1H), 4.13–4.20 (m, 2H), 6.07 (d, J = 9.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, CDCl$_3$) δ 0.2, 11.9, 16.3, 18.7, 19.6, 25.0, 29.7, 35.7, 37.7, 45.3, 53.4, 61.7, 66.2, 88.4, 108.3, 157.2, 174.6; HRMS (ESI-FTMS) m/z: [M + H]$^{+}$ calcd for C$_{19}$H$_{37}$N$_2$O$_4$Si 385.2517; found, 385.2519. Compound **12** upon slow evaporation from acetonitrile afforded a crystalline sample that was then examined by single-crystal X-ray diffraction (Bruker D8 Venture instrument using Cu Kα-radiation). The structure was determined and refined using Olex2 and SHELXT programs.

(2R,3R)-3-Ethyl-2-methyl-5-(trimethylsilyl)pent-4-ynoic acid (8). Following a literature procedure[17] with modifications, a solution of **2** (10.83 g, 33.5 mmol) in THF/water (3:1 ratio, 440 mL) at 0 °C was treated with a mixture of aqueous 0.5 M LiOH (100.5 mmol, 201 mL) and 30% H$_2$O$_2$ (268 mmol, 31 mL). The resulting solution was stirred at 0 °C for 1 h, then a cold solution of NaHSO$_3$ (prepared from 40 g of solid reagent in 250 mL of cold water) was added. The solution was then acidified by addition of cold concentrated HCl until pH 1. Both tasks were done as quickly as possible (<5 min) while the solution was maintained at 0 °C. The mixture after acidification was quickly extracted with ethyl acetate (3 × 200 mL). The combined organic extract was dried (Na$_2$SO$_4$), concentrated under reduced pressure, and purified by passage through a silica pad [hexanes/ethyl acetate (7:1)] to afford a yellow oil (6.82 g, 96%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.14 (s, 9H), 1.02 (t, J = 7.3 Hz, 3H), 1.23 (d, J = 6.6 Hz, 3H), 1.40–1.58 (m, 2H), 2.65–2.71 (m, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, CDCl$_3$) δ 0.2, 12.1, 13.5, 24.1, 37.3, 43.4, 87.4, 107.5, 180.6; HRMS (ESI-FTMS) m/z: [M + H]$^{+}$ calcd for C$_{11}$H$_{21}$O$_2$Si 213.1305; found, 213.1305.

(2R,3R)-3-Ethyl-N-methoxy-N,2-dimethyl-5-(trimethylsilyl)pent-4-ynamide (13). Following a literature procedure,[51] a solution of **8** (4.58 g, 21.6 mmol) in CH$_2$Cl$_2$ (43 mL) at 0 °C was treated with oxalyl chloride (3.65 mL, 43.2 mmol) and DMF (167 μL, 2.16 mmol). The reaction mixture was stirred at 0 °C for 10 min and room temperature for 1 h followed by concentration under reduced pressure to give a residue, which was then treated with anhydrous diethyl ether (43 mL). The resulting ethereal solution was then treated with a solution of N,O-dimethylhydroxyamine hydrochloride (4.21 g, 43.2 mmol), Na$_2$CO$_3$ (9.16 g, 86.4 mmol), and pyridine (174 μL, 2.16 mmol) in diethyl ether (86 mL) at 0 °C followed by stirring at room temperature for 15 h. Then, water (100 mL) was added. The ethereal layer was collected, and the aqueous layer was further extracted with diethyl ether (3 × 100 mL). The combined organic extract was dried (Na$_2$SO$_4$), concentrated under reduced pressure, and dried overnight under vacuum to afford a yellow oil (5.48 g, 99%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.11 (s, 9H), 1.02 (t, J = 7.3 Hz, 3H), 1.11 (d, J = 6.9 Hz, 3H), 1.32–1.41 (m, 1H), 1.60–1.68 (m, 1H), 2.64 (td, J = 9.4 and 4.0 Hz, 1H), 3.03 (br, 1H), 3.21 (s, 3H), 3.73 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, CDCl$_3$) δ 0.3, 11.4, 14.7, 23.7, 32.2, 36.8, 39.2, 61.6, 86.4, 109.0; one expected resonance is missing; HRMS (ESI-FTMS) m/z: [M + H]$^{+}$ calcd for C$_{13}$H$_{26}$NO$_2$Si 256.1727; found, 256.1724.

(3R,4R)-4-Ethyl-1-methoxy-3-methyl-6-(trimethylsilyl)hex-5-yn-2-one (14-OMe). Following a general procedure,[53] a solution of **Sn-Me** (184 mg, 0.55 mmol) in THF (1.0 mL) at −78 °C was treated with n-BuLi (1.6 M in hexanes, 344 μL, 0.55 mmol). The resulting mixture was stirred at −78 °C for 10 min, then a solution of **13** (64.0 mg, 0.25 mmol) in THF (200 μL) was added slowly (1 min). The reaction mixture was stirred at −78 °C for 35 min followed by the addition of saturated aqueous NH$_4$Cl solution (1.5 mL). The mixture was allowed to warm to room temperature and then extracted with Et$_2$O (3 × 2.0 mL). The combined organic extract was dried (Na$_2$SO$_4$), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (10:1)] to give a colorless oil (32 mg, 54%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.13 (s, 9H), 1.00 (t, J = 7.3 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 1.34 (ddq, J = 14.5, 9.4, and 7.4 Hz, 1H), 1.57 (dtd, J = 14.8, 7.3, and 4.1 Hz, 1H), 2.54 (td, J = 9.1, 4.0 Hz, 1H), 2.64–2.74 (m, 1H), 3.43 (s, 3H), 4.11–4.25 (m, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, CDCl$_3$) δ 0.2, 11.4, 13.8, 24.2, 36.6, 46.0, 59.4, 77.6, 87.6, 108.0, 210.1; HRMS (ESI-FTMS) m/z: [M + H]$^{+}$ calcd for C$_{13}$H$_{25}$O$_2$Si 241.1618; found, 241.1615.

(3R,4R)-4-Ethyl-1-((2-(trimethylsilyl)ethoxy)methoxy)-3-methyl-6-(trimethylsilyl)hex-5-yn-2-one (14-OSEM). Following a general procedure,[53] a solution of **Sn-SEM** (248 mg, 0.55 mmol) in distilled THF (1.0 mL) at −78 °C was treated with n-BuLi (1.6 M in hexanes, 344 μL, 0.55 mmol). The resulting mixture was stirred at −78 °C for 10 min, then a solution of **13** (64.0 mg, 0.25 mmol) in distilled THF (200 μL) was added slowly (1 min). The reaction mixture was stirred at −78 °C for 25 min followed by the addition of saturated aqueous NH$_4$Cl solution (1.5 mL). The mixture was allowed to warm to room temperature and then extracted with Et$_2$O (3 × 2.0 mL). The combined organic extract was dried (Na$_2$SO$_4$), concentrated, and chromatographed [silica, hexanes/ethyl acetate (10:1)] to give a colorless oil (58 mg, 65%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.01 (s, 9H), 0.13 (s, 9H), 0.91–0.94 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H), 1.33 (ddt, J = 14.5, 9.4, and 7.2 Hz, 1H), 1.55 (dtd, J = 14.6, 7.4, and 4.3 Hz, 1H), 2.55–2.59 (m, 1H), 2.68–2.74 (m, 1H), 3.61–3.69 (m, 2H), 4.28–4.36 (m, 2H), 4.71–4.74 (m, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, CDCl$_3$) δ −1.3, 0.2, 11.5, 13.7, 18.2, 24.2, 36.5, 46.4, 65.8, 72.3, 87.5, 95.0, 107.9, 209.5; HRMS (ESI-FTMS) m/z: [M + H]$^{+}$ calcd for C$_{18}$H$_{37}$O$_3$Si$_2$ 357.2276; found, 357.2269.

(3R,4R)-4-Ethyl-1-(methoxymethoxy)-3-methyl-6-(trimethylsilyl)hex-5-yn-2-one (14-OMOM). Following a general procedure,[53] a solution of **Sn-MOM** (209 mg, 0.55 mmol) in distilled THF (1.0 mL) at −78 °C was treated with n-BuLi (1.6 M in hexanes, 344 μL, 0.55 mmol). The resulting mixture was stirred at −78 °C for 10 min, then a solution of **13** (64.0 mg, 0.25 mmol) in distilled THF (200 μL) was added slowly (1 min). The reaction mixture was stirred at −78 °C for 25 min followed by the addition of saturated aqueous NH$_4$Cl solution (1.5 mL). The mixture was allowed to warm to room temperature and then extracted with Et$_2$O (3 × 2.0 mL). The combined organic extract was dried (Na$_2$SO$_4$), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (10:1)] to give a colorless oil (41.4 mg, 61%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.12 (s, 9H), 1.00 (t, J = 7.4 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H), 1.30–1.39 (m, 1H),

1.57 (ddh, J = 14.7, 7.4, and 4.0 Hz, 1H), 2.55 (td, J = 9.0 and 4.0 Hz, 1H), 2.67–2.73 (m, 1H), 3.38 (s, 3H), 4.29 (d, J = 17.7 Hz, 1H), 4.35 (d, J = 17.7 Hz, 1H), 4.68 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 0.2, 11.4, 13.8, 24.2, 36.5, 46.4, 55.8, 72.1, 87.6, 96.6, 107.8, 209.5; HRMS (ESI-FTMS) m/z: [M + H]$^+$ calcd for C$_{14}$H$_{27}$O$_3$Si 271.1724; found, 271.1716.

(3R,4R)-1-(Benzyloxy)-4-ethyl-3-methyl-6-(trimethylsilyl)hex-5-yn-2-one (14-OBn). Following a general procedure,[53] a solution of **Sn-Bn** (206 mg, 0.50 mmol) in THF (1.0 mL) at −78 °C was treated with n-BuLi (1.6 M in hexanes, 313 μL, 0.50 mmol). The resulting mixture was stirred at −78 °C for 10 min, then a solution of **13** (64.0 mg, 0.25 mmol) in THF (200 μL) was added slowly (1 min). The reaction mixture was stirred at −78 °C for 20 min followed by the addition of saturated aqueous NH$_4$Cl solution (1.5 mL). The mixture was allowed to warm to room temperature and then extracted with Et$_2$O (3 × 1.5 mL). The combined organic extract was dried (Na$_2$SO$_4$), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (10 : 1)] to give a colorless oil (35 mg, 44%): ^{1}H NMR (600 MHz, CDCl$_3$) δ 0.12 (s, 9H), 1.00 (t, J = 7.4 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 1.34 (ddq, J = 14.2, 9.1, and 7.3 Hz, 1H), 1.56 (dtd, J = 14.7, 7.4, and 4.1 Hz, 1H), 2.57 (td, J = 9.2 and 4.0 Hz, 1H), 2.76 (p, J = 7.2 Hz, 1H), 4.21 (d, J = 17.4 Hz, 1H), 4.26 (d, J = 17.5 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.63 (d, J = 11.8 Hz, 1H), 7.28–7.40 (m, 5H); ^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$) δ 0.2, 11.4, 13.7, 24.2, 36.4, 46.1, 73.5, 75.1, 87.4, 108.1, 128.05, 128.08, 128.6, 137.5, 210.2; HRMS (ESI-FTMS) m/z: [M + H]$^+$ calcd for C$_{19}$H$_{29}$O$_2$Si 317.1931; found, 317.1927.

(3R,4R)-4-Ethyl-1-((2-methoxyethoxy)methoxy)-3-methyl-6-(trimethylsilyl)hex-5-yn-2-one (14-OMEM). Following a general procedure,[53] a solution of **Sn-MEM** (4.46 g, 10.9 mmol) in distilled THF (44 mL) at −78 °C was treated with n-BuLi (2.5 M in hexanes, 4.36 mL, 10.9 mmol). The resulting mixture was stirred at −78 °C for 10 min, then a solution of **13** (1.39 g, 5.45 mmol) in distilled THF (4.28 mL) was added slowly (5 min). The reaction mixture was stirred at −78 °C for 35 min followed by the addition of saturated aqueous NH$_4$Cl solution (70 mL). The mixture was allowed to warm to room temperature and then extracted with Et$_2$O (3 × 40 mL). The combined organic extract was dried (Na$_2$SO$_4$), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (10 : 1)] to give a colorless oil (1.27 g, 74%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.12 (s, 9H), 1.00 (t, J = 7.3 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H), 1.29–1.38 (m, 1H), 1.55 (dddd, J = 14.8, 11.4, 6.6, and 4.1 Hz, 1H), 2.56 (ddd, J = 9.7, 8.2, and 4.0 Hz, 1H), 2.69 (quint, J = 7.0 Hz, 1H), 3.38 (s, 3H), 3.54 (t, J = 4.7 Hz, 2H), 3.70–3.77 (m, 2H), 4.31–4.38 (m, 2H), 4.76–4.79 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 0.2, 11.4, 13.7, 24.2, 36.5, 46.4, 59.1, 67.4, 71.8, 72.3, 87.5, 95.7, 107.9, 209.3; HRMS (ESI-FTMS) m/z: [M + H]$^+$ calcd for C$_{16}$H$_{31}$O$_4$Si 315.1986; found, 315.1982.

(3R,4R)-4-Ethyl-3-methyl-1-((tetrahydro-2H-pyran-2-yl)oxy)-6-(trimethylsilyl)hex-5-yn-2-one (14-OTHP). Following a general procedure,[53] a solution of **Sn-THP** (4.46 g, 11.0 mmol) in distilled THF (20 mL) at −78 °C was treated with n-BuLi (1.6 M in hexanes, 6.88 mL, 11.0 mmol) and stirred for 10 min. Then, a solution of **13** (1.28 g, 5.00 mmol) in distilled

THF (4.0 mL) was added slowly (5 min). The reaction mixture was stirred at −78 °C for 15 min followed by the addition of saturated aqueous NH$_4$Cl solution (30 mL). The mixture was allowed to warm to room temperature and then extracted with Et$_2$O (3 × 25 mL). The combined organic extract was dried (Na$_2$SO$_4$), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (10 : 1)] to give two fractions.

Fraction 1 (1.08 g, 70%) was identified as the title compound comprised of a mixture of two inseparable diastereomers of which the ^{1}H NMR spectra are overlapped: ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.13 (two singlets, 9H), 1.00 (t, J = 7.3 Hz, 3H), 1.10 (two doublets, J = 7.0 Hz for each, 3H), 1.30–1.39 (m, 1H), 1.52–1.63 (m, 4H), 1.70–1.80 (m, 2H), 1.83–1.91 (m, 1H), 2.58 (dddd, J = 9.8, 8.1, 5.9, and 4.0 Hz, 1H), 2.71–2.81 (m, 1H), 3.49–3.53 (m, 1H), 3.81–3.86 (m, 1H), 4.26–4.43 (m, 2H), 4.66 (t, J = 3.5 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 0.20, 0.22, 11.4, 11.5, 13.6, 13.7, 19.2, 24.1, 24.2, 25.5, 30.4, 36.4, 46.32, 46.33, 62.2, 62.3, 71.8, 71.9, 87.4, 98.7, 108.0, 108.1, 210.0, 210.1; HRMS (ESI-FTMS) m/z: [M + Na]$^+$ calcd for C$_{17}$H$_{30}$O$_3$SiNa 333.1856; found, 333.1849.

Fraction 2 (289 mg, 24%) was identified as the desilylated derivative of the desired product (**14-OTHP-desTMS**), comprised of a mixture of two inseparable diastereomers of which the ^{1}H NMR spectra are overlapped: ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.03 (t, J = 7.3 Hz, 3H), 1.12 (two doublets, J = 7.0 Hz for each, 3H), 1.34–1.43 (m, 1H), 1.52–1.64 (m, 4H), 1.70–1.81 (m, 2H), 1.83–1.90 (m, 1H), 2.09–2.10 (m, 1H), 2.56–2.62 (m, 1H), 2.75–2.85 (m, 1H), 3.48–3.53 (m, 1H), 3.81–3.87 (m, 1H), 4.25–4.42 (m, 2H), 4.66–4.68 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 11.4, 11.5, 13.75, 13.77, 19.15, 19.19, 24.1, 25.45, 25.47, 30.3, 30.4, 35.2, 35.3, 45.9, 46.0, 62.27, 62.32, 70.98, 71.04, 71.7, 71.8, 85.4, 85.5, 98.6, 98.7, 210.07, 210.09; HRMS (ESI-FTMS) m/z: [M + Na]$^+$ calcd for C$_{14}$H$_{22}$O$_3$Na 261.1461; found, 261.1459.

(3R,4R)-4-Ethyl-1-hydroxy-3-methyl-6-(trimethylsilyl)hex-5-yn-2-one (14-OH). From **14-OTHP**: a solution of **14-OTHP** (42.5 mg, 137 μmol) in anhydrous methanol (780 μL) was treated with Amberlyst 15 (18.8 mg). The reaction mixture was stirred at room temperature for 15 h and then filtered through a Celite pad with multiple washes with CH$_2$Cl$_2$. The resulting filtrate was concentrated under reduced pressure and dried under vacuum to give a light-yellow oil (29 mg, 93%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.13 (s, 9H), 1.01 (t, J = 7.3 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H), 1.32–1.41 (m, 1H), 1.58 (dqd, J = 14.6, 7.3, and 4.1 Hz, 1H), 2.55 (td, J = 8.9, 4.0 Hz, 1H), 2.64 (dt, J = 13.9 and 7.2 Hz, 1H), 2.81 (brs, 1H), 4.33 (d, J = 19.2 Hz, 1H), 4.39 (d, J = 19.2 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 0.1, 11.4, 14.0, 24.5, 37.0, 46.4, 68.4, 88.2, 107.2, 212.3; HRMS (ESI-FTMS) m/z: [M + H]$^+$ calcd for C$_{12}$H$_{23}$O$_2$Si 227.1462; found, 227.1464.

From **14-OMEM**: a solution of **14-OMEM** (393.4 mg, 1.25 mmol) in CH$_2$Cl$_2$ (20 mL) was treated with anhydrous ZnBr$_2$ (638.0 mg, 2.50 mmol). The reaction mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure. The crude material was purified by chromatography (silica, CH$_2$Cl$_2$) to afford a colorless oil (203 mg, 72%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.13 (s, 9H), 1.01 (t, J = 7.4 Hz, 3H),

1.14 (d, J = 6.9 Hz, 3H), 1.32–1.41 (m, 1H), 1.53–1.61 (m, 1H), 2.52–2.56 (m, 1H), 2.61–2.67 (m, 1H), 3.12 (t, J = 4.7 Hz, 1H), 4.30–4.41 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 0.1, 11.4, 13.9, 24.5, 37.0, 46.4, 68.4, 88.2, 107.2, 212.3; HRMS (ESI-FTMS) m/z: [M + H]$^+$ calcd for C$_{12}$H$_{23}$O$_2$Si 227.1462; found, 227.1459.

(2R,3R)-1-(1,3-Dithian-2-yl)-3-ethyl-2-methyl-5-(trimethylsilyl) pent-4-yn-1-one (15). Following a reported procedure,[63] a solution of 1,3-dithiane (180.4 mg, 1.500 mmol) in 3 mL of freshly distilled THF at −78 °C under argon was treated dropwise with n-BuLi (630 μL, 1.6 mmol, 2.5 M in hexanes) for 5 min. The resulting mixture was allowed to warm to −20 °C and stirred for 1 h under argon. The reaction mixture was then cooled to −78 °C, treated dropwise with a solution of **13** (255.4 mg, 0.9999 mmol) in 1 mL of freshly distilled THF, and stirred at −78 °C for 30 min before switching to a bath at −20 °C. The resulting solution was allowed to stir at −20 °C until the starting material disappeared (on the basis of TLC analysis) before the addition of saturated aqueous NH$_4$Cl solution (5 mL). The mixture was extracted with CH$_2$Cl$_2$ (4 × 3 mL). The combined organic extract was dried (Na$_2$SO$_4$), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (50 : 1)] to obtain a colorless oil (251.0 mg, 80%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.14 (s, 9H), 1.01 (t, J = 7.4 Hz, 3H), 1.17 (d, J = 6.7 Hz, 3H), 1.45–1.30 (m, 1H), 1.63 (dt, J = 13.4, 7.4, and 3.7 Hz, 1H), 2.06–1.95 (m, 1H), 2.11 (dddd, J = 11.1, 5.2, 4.0, and 2.7 Hz, 1H), 2.65–2.42 (m, 3H), 3.00–2.89 (m, 2H), 3.39 (ddd, J = 14.2, 12.0, and 2.7 Hz, 1H), 4.45 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 0.2, 11.2, 15.3, 24.4, 25.4, 25.9, 26.0, 37.6, 47.3, 47.7, 88.2, 107.6, 204.4; HRMS (ESI-FTMS) m/z: [M + H]$^+$ calcd for C$_{15}$H$_{27}$OS$_2$Si 315.1267; found, 315.1265.

(3R,4R)-4-Ethyl-1-methoxy-3-methyl-1-(phenylthio)-6-(trimethyl-silyl)hex-5-yn-2-one (16). Following a reported procedure,[64] a solution of (methoxymethyl)(phenyl)sulfane (231.3 mg, 1.500 mmol) in 10 mL of freshly distilled THF at −78 °C under argon was treated dropwise with n-BuLi (600 μL, 1.5 mmol, 2.5 M in hexanes) for 5 min, and stirred for 1 h at the same condition. Then, the resulting solution was treated dropwise with a solution of **13** (255.4 mg, 0.9999 mmol) in 10 mL of freshly distilled THF, and stirred at −78 °C. The reaction flask was allowed to warm overnight to room temperature. The reaction mixture was treated with saturated aqueous NH$_4$Cl solution (15 mL), and the resulting mixture was extracted with CH$_2$Cl$_2$ (4 × 20 mL). The combined organic extract was dried (Na$_2$SO$_4$), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (15 : 1)] to obtain a light-yellow oil (148.2 mg, 43%).^{1}H NMR (500 MHz, CDCl$_3$) δ 0.89–0.85 (m, 9H for each epimer), 1.25–1.15 (m, 1H for each epimer), 1.38–1.31 (m, 1H, minor epimer), 1.52–1.44 (m, 1H, major epimer), 2.29–2.25 (m, 1H, major epimer), 2.52–2.48 (m, 1H, minor epimer), 2.97–2.87 (m, 1H for each epimer), 3.45 (s, 3H, minor epimer), 3.49 (s, 3H, major epimer), 5.04 (s, 1H, minor epimer), 5.23 (s, 1H, major epimer), 7.18–7.13 (m, 3H for each epimer), 7.32–7.30 (m, 2H, major epimer), 7.44–7.40 (m, 2H, minor epimer); ^{13}C NMR (125 MHz, CDCl$_3$, for the major epimer only) δ 0.0, 10.8, 13.7, 24.1, 37.5, 45.1, 56.2, 92.1, 107.5, 128.0, 128.9, 131.7, 132.5, 133.4, 202.6; HRMS (ESI-FTMS) m/z: [M + H]$^+$ calcd for C$_{19}$H$_{29}$O$_2$Si 349.1652; found, 349.1647.

(7R,11R,E)-3,7,11,15-Tetramethylhexadec-2-en-1-yl (4S,5S)-5-methyl-4-(2-((tetrahydro-2H-pyran-2-yl)oxy)acetyl)hept-6-ynoate (17). Following a standard method for esterification,[77] a solution of **29** (1.18 g, 4.18 mmol) and native (E,7R,11R)-3,7,11,15-tetramethylhexadec-2-en-1-ol (1.30 g, 4.39 mmol) in CH$_2$Cl$_2$ (20 mL) was treated with EDC (801.3 mg, 4.18 mmol) and DMAP (562.0 mg). The resulting mixture was stirred at room temperature for 12 h, followed by dilution with additional CH$_2$Cl$_2$ (80 mL). The organic solution was washed (0.5 M aqueous HCl (45 mL) and water (45 mL)), dried (Na$_2$SO$_4$), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (3 : 1)] to afford a light-yellow oil (1.43 g, 61%): ^{1}H NMR (700 MHz, CDCl$_3$) δ 0.84–0.87 (m, 12H), 1.02–1.10 (m, 4H), 1.11–1.46 (m, 18H), 1.49–1.62 (m, 6H), 1.68 (s, 3H), 1.71–1.79 (m, 2H), 1.84–1.89 (m, 1H), 1.91–2.03 (m, 4H), 2.11 (t, J = 2.7 Hz, 1H), 2.22 (dtd, J = 16.0, 7.9, and 5.2 Hz, 1H), 2.31 (dddd, J = 16.1, 8.7, 6.0, and 3.8 Hz, 1H), 2.71–2.83 (m, 2H), 3.48–3.52 (m, 1H), 3.83 (tdd, J = 11.3, 9.0, and 3.0 Hz, 1H), 4.19–4.42 (m, 2H), 4.56–4.61 (m, 1H), 4.67 (dt, J = 9.2, 3.5 Hz, 1H), 5.30–5.32 (m, 1H); ^{13}C{^{1}H} NMR (175 MHz, CDCl$_3$) δ 16.5, 17.9, 18.0, 19.16, 19.19, 19.86, 19.90, 22.8, 22.9, 23.7, 23.9, 24.6, 24.9, 25.2, 25.4, 25.5, 27.4, 27.5, 28.1, 30.3, 31.88, 31.90, 32.8, 33.0, 36.8, 37.4, 37.5, 37.6, 39.5, 40.0, 51.46, 51.53, 61.7, 62.27, 62.30, 70.4, 70.5, 73.0, 73.1, 86.1, 86.2, 98.6, 98.8, 118.01, 118.04, 143.06, 143.11, 172.90, 172.93, 209.6, 209.7; HRMS (ESI-FTMS) m/z: [M + H]$^+$ calcd for C$_{35}$H$_{61}$O$_5$ 561.4514; found, 561.4521.

2,5-Dioxopyrrolidin-1-yl 6-(($tert$-butyldiphenylsilyl)oxy)hexa-noate (18)

Method A. A literature route[26] was modified to derivatize pentan-1,5-diol in a streamlined four-step synthesis at a larger scale.

In the first step, a sample of NaH (60% dispersion in mineral oil, 10.00 g, 250 mmol) after being washed with hexanes (3 × 50 mL) was suspended in freshly distilled THF (500 mL). The resulting suspension under argon with stirring was treated dropwise with pentan-1,5-diol (26.04 g, 250 mmol) through an addition funnel. The reaction mixture was stirred at room temperature for 45 min, then $tert$-butyldiphenylsilyl chloride (68.72 g, 250 mmol) was added dropwise through an addition funnel. The resulting mixture was further stirred at room temperature for 1 h, treated with water (500 mL), and extracted with Et$_2$O (3 × 250 mL). The combined organic extract was dried (Na$_2$SO$_4$) and concentrated under reduced pressure to afford the crude 5-(($tert$-butyldiphenylsilyl)oxy)pentan-1-ol as a yellow oil (85.14 g).

In the second step, the entire crude sample from the first step was dissolved in CH$_2$Cl$_2$ (1.2 L) followed by treatment with DMP (116.64 g, 275 mmol) in one batch. The reaction mixture was stirred at room temperature for 1 h, then 10% aqueous Na$_2$S$_2$O$_3$ solution (800 mL) was added. The organic phase was collected, washed with saturated aqueous NaHCO$_3$ solution (800 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure to give the crude 5-(($tert$-butyldiphenylsilyl)oxy)pen-tanal as a yellow oil (90.10 g).

In the third step, the entire crude sample from the second step was dissolved in $tert$-butanol (600 mL) and water (200 mL)

followed by addition of 2-methyl-2-butene (264.8 mL, 2.5 mol), $NaH_2PO_4 \cdot H_2O$ (103.49 g, 750 mmol), and $NaClO_2$ (84.79 g, 750 mmol). The reaction mixture was stirred at room temperature for 30 min, diluted with brine solution (500 mL), acidified by adding 2 M aqueous HCl until pH 1, and extracted with ethyl acetate (3 × 250 mL). The combined organic extract was dried (Na_2SO_4) and concentrated under reduced pressure to give a residue, which upon dilution with CH_2Cl_2 gave rise to insoluble materials. Filtration through an F-fritted funnel followed by concentration under reduced pressure afforded the crude 5-((tert-butyldiphenylsilyl)oxy)pentanoic acid as a yellow oil (98.12 g).

In the final step, the entire crude sample from the third step was dissolved in CH_2Cl_2 (1 L) followed by addition of N-hydroxysuccinimide (34.53 g, 300 mmol). The solution was cooled at 0 °C, treated with DCC (61.90 g, 300 mmol), and stirred at 0 °C for 1 h and then at room temperature for 29 h, whereupon a white suspension was present. The reaction mixture was filtered. The filtered cake was washed with cold CH_2Cl_2. The filtrates were combined and concentrated under reduced pressure to give a thick yellow oil, which upon recrystallization in absolute ethanol (400 mL) afforded a white solid (75.34 g, 66% from 1,5-pentadiol): mp 57–60 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.06 (s, 9H), 1.64–1.71 (m, 2H), 1.87 (quint, J = 7.5 Hz, 2H), 2.61 (t, J = 7.5 Hz, 2H), 2.82 (br, 4H), 3.69 (t, J = 6.1 Hz, 2H), 7.36–7.44 (m, 6H), 7.67 (d, J = 6.4 Hz, 4H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 19.3, 21.3, 25.7, 27.0, 30.7, 31.6, 61.3, 127.8, 129.7, 133.9, 135.7, 168.7, 169.3; HRMS (ESI-FTMS) m/z: [M – H]$^-$ calcd for $C_{25}H_{30}NO_5Si$ 452.1899; found, 452.1916.

Method B. Following reported procedures[26,75] with modification, a mixture of pentan-1,5-diol (5.20 g, 49.9 mmol) and imidazole (4.90 g, 72.0 mmol) in anhydrous CH_2Cl_2 (250 mL) under argon at 0 °C was treated dropwise with a solution of tert-butyldiphenylsilyl chloride (16.55 g, 60.2 mmol) in anhydrous CH_2Cl_2 (75 mL) over 1 h. Then, the reaction mixture was allowed to warm overnight to room temperature. The mixture was treated with saturated aqueous NH$_4$Cl solution (150 mL). The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic extract was dried (Na_2SO_4) and concentrated under reduced pressure to obtain a crude yellow oil. The crude oil was used without any further purification. The oil was dissolved in anhydrous acetonitrile (100 mL) under argon at 0 °C. The solution was then treated with DIB (17.71 g, 55.0 mmol) and NHS (6.33 g, 55.0 mmol). The resulting reaction mixture was stirred for 0.5 h at 0 °C under argon. The mixture was filtered through a Celite pad. The filter cake was washed with ethyl acetate (3 × 100 mL). The filtrate was dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a colorless oil (5.90 g, 26%): ^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.05 (s, 9H), 1.64–1.69 (m, 2H), 1.84–1.90 (m, 2H), 2.61 (t, J = 7.5 Hz, 2H), 2.82–2.83 (m, 4H), 3.69 (t, J = 5 Hz, 2H), 7.37–7.43 (m, 6H), 7.65–7.67 (m, 4H); ^{13}C{^{1}H} NMR (CDCl$_3$, 125 MHz) δ 19.3, 21.3, 25.7, 27.0, 30.8, 31.6, 63.2, 127.8, 129.7, 133.9, 135.7, 168.7, 169.3.

(±)-3-Methoxy-1-trimethylsilylbutyne, Hexacarbonyldicobalt complex (19). Following a literature two-step procedure[17] but modified herein with the aim to streamline the synthesis, a solution of trimethylsilylacetylene (17.68 g, 180 mmol) in freshly distilled THF (300 mL) under argon was cooled at −78 °C followed by treatment with n-BuLi solution (1.6 M in hexanes, 118 mL, 190 mmol). The resulting solution was stirred at −78 °C for 10 min, then acetaldehyde (10.1 mL, 180 mmol) was added. After 15 min of stirring at −78 °C, the reaction mixture was treated with dimethyl sulfate (18.9 mL, 198 mmol), allowed to warm to room temperature, and stirred at room temperature for 24 h. Afterwards, the resulting opaque solution was treated with $Co_2(CO)_8$ (64.63 g, 189 mmol) in portions (gas evolution was noted upon addition of $Co_2(CO)_8$) followed by stirring at room temperature for another 24 h. Upon completion, the reaction mixture was treated with silica and then concentrated under reduced pressure. The sample impregnated on silica was subjected to short flash column chromatography [silica, 100% hexanes then hexanes/ethyl acetate (10:1)] to afford a dark brown solid (73.59 g, 92%): ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.31 (s, 9H), 1.47 (d, J = 6.2 Hz, 3H), 3.48 (s, 3H), 4.47 (q, J = 6.2 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 0.1, 23.0, 57.3, 78.0, 113.5, 200.5.

(R)-3-(5-((tert-Butyldiphenylsilyl)oxy)pentanoyl)-4-isopropyloxazolidin-2-one (20). Following a general procedure,[26] a solution of (R)-4-isopropyloxazolidin-2-one (10.34 g, 80.04 mmol) in freshly distilled THF (400 mL) at −78 °C under argon was treated with n-BuLi (2.5 M in hexanes, 32.0 mL, 80 mmol). After being stirred at −78 °C for 15 min, the reaction mixture was treated with a solution of **18** (36.31 g, 80.04 mmol) in THF (100 mL), allowed to warm to room temperature, and stirred at room temperature for 4 h. Upon completion, the reaction mixture was treated with saturated aqueous NH$_4$Cl solution (500 mL). The organic phase was collected. The aqueous phase was further extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (3:1)] to furnish a colorless oil (32.82 g, 88%): ^{1}H NMR (600 MHz, CDCl$_3$) δ 0.87 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 1.04 (s, 9H), 1.61–1.65 (m, 2H), 1.72–1.79 (m, 2H), 2.33–2.41 (m, 1H), 2.87 (ddd, J = 16.9, 8.1, and 6.8 Hz, 1H), 2.99 (ddd, J = 16.9, 8.2, and 6.6 Hz, 1H), 3.69 (t, J = 6.3 Hz, 2H), 4.20 (dd, J = 9.1 and 3.0 Hz, 1H), 4.25 (dd, J = 9.1 and 8.3 Hz, 1H), 4.43 (ddd, J = 8.3, 3.9, and 3.0 Hz, 1H), 7.36–7.43 (m, 6H), 7.66 (dd, J = 8.0 and 1.5 Hz, 4H); ^{13}C{^{1}H} NMR (150 Hz, CDCl$_3$) δ 14.8, 18.1, 19.4, 21.0, 27.0, 28.5, 32.1, 35.4, 58.5, 63.5, 63.7, 127.7, 129.7, 134.1, 135.7, 154.2, 173.3; HRMS (ESI-FTMS) m/z: [M + H]$^+$ calcd for $C_{27}H_{38}NO_4Si$ 468.2565; found, 468.2568.

(R)-3-((2S,3S)-2-(3-((tert-Butyldiphenylsilyl)oxy)propyl)-3-methyl-5-(trimethylsilyl)pent-4-ynoyl)-4-isopropyloxazolidin-2-one, Hexacarbonyldicobalt complex (21). Following a general procedure[26] with modifications, a solution of **20** (32.82 g, 70.18 mmol) in anhydrous CH_2Cl_2 (177 mL) at 0 °C under argon was treated with DIPEA (12.22 mL, 70.18 mmol) and Bu$_2$BOTf (1 M solution in CH_2Cl_2, 70.18 mL, 70 mmol). The resulting mixture was stirred at 0 °C for 15 min, then further Bu$_2$BOTf (35.09 mL, 35 mmol) was

added followed by immediate cooling to -78 °C. A solution of **19** (29.63 g, 70.18 mmol) in anhydrous CH_2Cl_2 (177 mL) was added to the reaction mixture at -78 °C *via* a cannula. The reaction mixture was stirred at -78 °C for 10 min, 0 °C for 30 min, and then room temperature for 30 min followed by treatment with pH 7 aqueous phosphate solution (0.1 M, 350 mL) and extraction with CH_2Cl_2 (3×200 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (7:1)] to afford a dark-red paste (55.59 g, 90%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.29 (s, 9H), 0.87 (d, $J = 6.9$ Hz, 3H), 0.93 (d, $J = 7.0$ Hz, 3H), 1.03 (s, 9H), 1.21 (d, $J = 7.1$ Hz, 3H), 1.47–1.56 (m, 3H), 2.01–2.07 (m, 1H), 2.29–2.34 (m, 1H), 3.40 (qd, $J = 7.1$ Hz and 2.3 Hz, 1H), 3.63 (t, $J = 6.5$ Hz, 2H), 4.09 (dt, $J = 11.9$ and 2.1 Hz, 1H), 4.19 (dd, $J = 9.1$ and 3.2 Hz, 1H), 4.25 (t, $J = 8.8$ Hz, 1H), 4.50 (dt, $J = 8.4$ and 3.4 Hz, 1H), 7.34–7.43 (m, 6H), 7.63–7.66 (m, 4H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 1.3, 14.7, 18.1, 18.4, 19.3, 20.9, 27.0, 28.7, 31.2, 41.5, 49.3, 58.4, 63.3, 64.3, 79.7, 115.2, 127.73, 127.74, 129.6, 134.0, 134.1, 135.7, 153.4, 173.9; HRMS (ESI-FTMS) m/z: $[M - H]^-$ calcd for $C_{40}H_{48}Co_2NO_{10}Si_2$ 876.1486; found, 876.1483.

(*R*)-3-((2*S*,3*S*)-2-(3-((*tert*-Butyldiphenylsilyl)oxy)propyl)-3-methyl-5-(trimethylsilyl)pent-4-ynoyl)-4-isopropyloxazolidin-2-one (22). Following a general procedure[26] with modifications, a solution of **21** (27.75 g, 31.61 mmol) in acetone (250 mL) was treated portionwise with ceric ammonium nitrate (dried under vacuum overnight, 69.32 g, 126.4 mmol). The resulting solution was stirred at room temperature for 30 min whereupon gas evolution no longer proceeded. The resulting solution was concentrated under reduced pressure, and the residue was diluted in water (350 mL) and CH_2Cl_2 (200 mL). The organic layer was collected. The aqueous layer was further extracted with CH_2Cl_2 (2×150 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and further dried overnight under vacuum to yield a yellow oil (18.62 g, 100%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.10 (s, 9H), 0.91 (dd, $J = 14.0$ and 6.9 Hz, 6H), 1.03 (s, 9H), 1.18 (d, $J = 7.1$ Hz, 3H), 1.32–1.41 (m, 1H), 1.43–1.58 (m, 2H), 1.73–1.77 (m, 2H), 2.38 (ddp, $J = 10.7$, 7.0, and 3.7 Hz, 1H), 2.91 (quint, $J = 7.1$ Hz, 1H), 3.62 (t, $J = 6.6$ Hz, 1H), 3.99 (q, $J = 7.0$ Hz, 1H), 4.16–4.21 (m, 2H), 4.44 (dt, $J = 7.5$ and 3.9 Hz, 1H), 7.36–7.43 (m, 6H), 7.64–7.65 (m, 4H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 15.1, 17.6, 18.2, 19.3, 25.2, 27.0, 28.69, 28.74, 29.7, 47.1, 58.8, 63.2, 63.8, 85.4, 109.5, 127.8, 129.7, 134.0, 135.70, 135.71, 153.7, 174.4; HRMS (ESI-FTMS) m/z: $[M + H]^+$ calcd for $C_{34}H_{50}NO_4Si_2$ 592.3273; found, 592.3274.

(2*S*,3*S*)-2-(3-((*tert*-Butyldiphenylsilyl)oxy)propyl)-3-methyl-5-(trimethylsilyl)pent-4-ynoic acid (23) and (2*S*,3*S*)-2-(3-((*tert*-butyldiphenylsilyl)oxy)propyl)-3-methylpent-4-ynoic acid (IVb). Following a literature procedure[17] with modifications, a solution of **22** (18.62 g, 31.46 mmol) in THF (300 mL) was cooled at 0 °C followed by addition of a pre-cooled solution of $LiOH \cdot H_2O$ (3.96 g, 94.38 mmol) and 30% H_2O_2 (25.7 mL, 251.7 mmol) in water (100 mL). The reaction mixture was stirred at 0 °C for 2 days followed by treatment with saturated aqueous $NaHSO_3$ solution until a negative response showed by KI/starch paper. The resulting mixture was treated with 2 M aqueous HCl until pH 1 and then extracted with ethyl acetate (3×200 mL). The combined organic extract was dried

(Na_2SO_4), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (5:1) with 2% (v/v) AcOH] to afford two fractions.

Fraction 1 (colorless oil) was characterized as **23** (11.34 g, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.04 (s, 9H), 1.20 (d, $J = 7.0$ Hz, 3H), 1.53–1.68 (m, 2H), 1.69–1.78 (m, 2H), 2.47 (ddd, $J = 9.2$, 6.6, and 5.1 Hz, 1H), 2.80 (quint, $J = 7.0$ Hz, 1H), 3.67 (tq, $J = 6.9$ and 3.9 Hz, 2H), 7.36–7.43 (m, 6H), 7.66 (dd, $J = 8.0$ and 1.6 Hz, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 0.2, 18.0, 19.3, 25.5, 27.0, 29.3, 30.6, 50.5, 63.7, 86.3, 108.6, 127.8, 127.9, 129.7, 129.8, 134.01, 134.03, 134.9, 135.7; HRMS (ESI-FTMS) m/z: $[M + H]^+$ calcd for $C_{28}H_{41}O_3Si_2$ 481.2589; found, 481.2587.

Fraction 2 (yellow oil) was characterized as **IVb** (2.22 g, 17%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.23 (d, $J = 7.2$ Hz, 3H), 1.53–1.69 (m, 2H), 1.71–1.83 (m, 2H), 2.10 (d, $J = 2.5$ Hz, 1H), 2.48 (ddd, $J = 9.8$, 6.6, and 4.6 Hz, 1H), 2.81 (quintd, $J = 7.0$ and 2.5 Hz, 1H), 3.68 (qd, $J = 10.2$ and 6.0 Hz, 2H), 7.36–7.43 (m, 6H), 7.66 (dd, $J = 8.0$ and 1.6 Hz, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 18.0, 19.3, 25.5, 27.0, 28.1, 30.4, 50.0, 63.5, 70.1, 86.0, 127.8, 129.7, 134.0, 135.7, 179.1; HRMS (ESI-FTMS) m/z: $[M + H]^+$ calcd for $C_{25}H_{33}O_3Si_2$ 409.2194; found, 409.2202.

(2*S*,3*S*)-2-(3-((*tert*-Butyldiphenylsilyl)oxy)propyl)-*N*-methoxy-*N*,3-dimethyl-5-(trimethylsilyl)pent-4-ynamide (24). Following a general procedure,[51] a solution of **23** (11.34 g, 23.59 mmol) in CH_2Cl_2 (47 mL) at 0 °C was treated with oxalyl chloride (5.99 g, 47.2 mmol) and DMF (183 μL, 2.36 mmol). The reaction mixture was stirred at 0 °C for 10 min and then room temperature for 1 h followed by concentration under reduced pressure to remove all volatile species. The resulting residue was dissolved in anhydrous Et_2O (47 mL) and then added to a suspension of *N,O*-dimethylhydroxyamine hydrochloride (4.60 g, 47.18 mmol), Na_2CO_3 (10.00 g, 94.36 mmol), and pyridine (187 μL, 2.36 mmol) in anhydrous Et_2O (94 mL) at 0 °C. The resulting mixture was stirred at room temperature for 15 h followed by addition of water (200 mL) and extraction with Et_2O (3×100 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a colorless oil (10.01 g, 81%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 0.11 (s, 9H), 1.04 (s, 9H), 1.20 (d, $J = 7.0$ Hz, 3H), 1.48–1.60 (m, 3H), 1.76 (dtd, $J = 12.9$, 6.3, and 2.9 Hz, 1H), 2.76 (dq, $J = 9.0$ and 7.0 Hz, 1H), 2.91 (br, 1H), 3.19 (s, 3H), 3.60–3.67 (m, 2H), 3.69 (s, 3H), 7.36–7.38 (m, 4H), 7.40–7.42 (m, 2H), 7.64–7.66 (m, 4H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 18.1, 19.4, 25.9, 27.0, 29.3, 30.4, 32.1, 45.9, 61.5, 63.8, 85.0, 127.7, 129.7, 134.1, 134.2, 135.7, 175.8; HRMS (ESI-FTMS) m/z: $[M + H]^+$ calcd for $C_{30}H_{46}NO_3Si_2$ 524.3011; found, 524.3019.

(2*S*,3*S*)-2-(3-((*tert*-Butyldiphenylsilyl)oxy)propyl)-*N*-methoxy-*N*,3-dimethylpent-4-ynamide (25). A solution of **IVb** (694.9 mg, 1.70 mmol) in CH_2Cl_2 (3.40 mL) at 0 °C was treated with oxalyl chloride (288 μL, 3.40 mmol) and DMF (13 μL, 0.17 mmol). The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 1 h followed by concentration to remove all volatile species. The resulting residue was dissolved in Et_2O (3.40 mL) and then added to a suspension of *N,O*-

dimethylhydroxyamine hydrochloride (331.7 mg, 3.40 mmol), Na_2CO_3 (720.7 mg, 6.80 mmol), and pyridine (14 μL, 0.17 mmol) in Et_2O (6.80 mL) at 0 °C. The resulting mixture was stirred at room temperature for 15 h followed by the addition of water (15 mL) and extraction with Et_2O (3 × 10 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a colorless oil (638.8 mg, 86%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.22 (d, J = 7.0 Hz, 3H), 1.48–1.57 (m, 2H), 1.62–1.68 (m, 1H), 1.77–1.83 (m, 1H), 2.06 (d, J = 1.2 Hz, 1H), 2.75–2.81 (m, 1H), 2.94 (br s, 1H), 3.20 (s, 3H), 3.61–3.72 (m, 5H), 7.36–7.43 (m, 6H), 7.66 (d, J = 6.5 Hz, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.0, 19.4, 25.8, 27.0, 28.0, 30.3, 32.1, 45.5, 61.5, 63.7, 69.2, 87.6, 127.7, 129.7, 134.0, 134.1, 135.7, 175.5; HRMS (ESI-FTMS) m/z: [M + H][+] calcd for $C_{27}H_{38}NO_3Si$ 452.2616; found, 452.2627.

(3S,4S)-3-(3-((tert-Butyldiphenylsilyl)oxy)propyl)-4-methyl-1-((tetrahydro-2H-pyran-2-yl)oxy)-6-(trimethylsilyl)hex-5-yn-2-one (26). Following a general procedure,[53] a solution of **Sn-THP** (19.36 g, 47.78 mmol) in freshly distilled THF (75 mL) was degassed by a freeze–pump–thaw protocol (3 cycles) followed by cooling at −78 °C. A sample of n-BuLi (1.6 M in hexanes, 29.9 mL, 48 mmol) was added, and the resulting mixture was stirred at −78 °C for 5 min. The mixture containing in situ generated ((tetrahydro-2H-pyran-2-yl)oxy)methyl lithium, still at −78 °C, was treated with a solution of **24** (10.01 g, 19.11 mmol) in THF (15.5 mL, degassed in advance by bubbling with argon in 30 min) followed by stirring at −78 °C for 15 min. Upon completion, the reaction mixture was treated with saturated aqueous NH_4Cl solution (100 mL) and extracted with Et_2O (3 × 75 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed [silica, hexanes 100% to hexanes/ethyl acetate (92:8)] to give a colorless thick oil (7.03 g, 64%) consisting of two inseparable diastereomers (due to the presence of the THP unit): ^{1}H NMR (700 MHz, $CDCl_3$) δ 0.13 (s, 9H), 1.04 (s, 9H), 1.16 (d, J = 6.9 Hz, 3H), 1.43–1.62 (m, 5H), 1.66–1.71 (m, 2H), 1.72–1.78 (m, 2H), 1.83–1.91 (m, 1H), 2.59–2.71 (m, 2H), 3.47–3.51 (m, 1H), 3.59–3.65 (m, 2H), 3.80–3.84 (m, 1H), 4.21–4.41 (m, 2H), 4.65 (dt, J = 9.2 and 3.5 Hz, 1H), 7.38 (t, J = 7.4 Hz, 4H), 7.42 (t, J = 7.2 Hz, 2H), 7.65 (t, J = 6.9 Hz, 4H); ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 18.31, 18.33, 19.1, 19.2, 19.3, 25.49, 25.51, 25.53, 27.0, 28.67, 28.70, 30.30, 30.35, 30.4, 53.2, 53.6, 62.1, 62.2, 63.7, 72.8, 73.1, 86.26, 86.30, 98.5, 98.7, 109.2, 109.3, 127.8, 129.7, 133.97, 134.01, 135.7, 209.9, 210.1; HRMS (ESI-FTMS) m/z: [M + H][+] calcd for $C_{34}H_{51}O_4Si_2$ 579.3320; found, 579.3316.

(3S,4S)-3-(3-((tert-Butyldiphenylsilyl)oxy)propyl)-4-methyl-1-((tetrahydro-2H-pyran-2-yl)oxy)hex-5-yn-2-one (27). A solution of **Sn-THP** (324.2 mg, 0.80 mmol) in freshly distilled THF (1.0 mL) was degassed by a freeze–pump–thaw protocol (3 cycles) followed by cooling at −78 °C. A sample of n-BuLi (1.6M in hexanes, 500 μL, 0.80 mmol) was added, and the resulting mixture was stirred at −78 °C for 5 min. The mixture containing in situ generated ((tetrahydro-2H-pyran-2-yl)oxy)methyl lithium, still at −78 °C, was treated with a solution of **25** (87.1 mg, 0.20 mmol) followed by stirring at −78 °C for 15 min. Then, the reaction mixture was treated with saturated aqueous NH_4Cl

solution (1.5 mL) and extracted with Et_2O (3 × 1.5 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (3:1)] to give a colorless oil (33.7 mg, 34%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.19 (d, J = 6.6 Hz, 3H), 1.41–1.93 (m, 10H), 2.09–2.10 (m, 1H), 2.63–2.75 (m, 2H), 3.46–3.51 (m, 1H), 3.59–3.67 (m, 2H), 3.79–3.86 (m, 1H), 4.18–4.42 (m, 2H), 4.65–4.67 (m, 1H), 7.36–7.44 (m, 6H), 7.60–7.71 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.1, 18.2, 19.10, 19.14, 19.3, 25.3, 25.36, 25.43, 25.5, 27.0, 27.4, 27.5, 30.2, 30.3, 52.5, 52.6, 62.1, 62.2, 63.6, 70.1, 70.2, 72.8, 73.0, 86.5, 86.6, 98.46, 98.50, 127.8, 129.7, 133.90, 133.94, 135.7, 209.96, 210.03; HRMS (ESI-FTMS) m/z: [M + Na][+] calcd for $C_{31}H_{42}O_4SiNa$ 529.2745; found, 529.2741.

(4S,5S)-5-Methyl-4-(2-((tetrahydro-2H-pyran-2-yl)oxy)acetyl)hept-6-ynoic acid (29). A sample of **26** (7.03 g, 12.1 mmol) was treated with pre-cooled TBAF (1 M solution in THF, 66.0 mL), and the resulting solution was stirred at 0 °C for 3 h. Upon completion, the reaction mixture was diluted in saturated aqueous NH_4Cl solution (100 mL) followed by extraction with CH_2Cl_2 (3 × 100 mL). The combined organic extract was dried and concentrated under reduced pressure to give a residue, which was used directly in the next step. The entire crude sample in acetonitrile/water (1:1, 26 mL) at 0 °C was treated with DIB (8.60 g, 26.71 mmol) and TEMPO (189.1 mg, 1.21 mmol). The reaction mixture was stirred at 0 °C for 2 days followed by addition of 5% aqueous $Na_2S_2O_3$ solution (130 mL) and extraction with ethyl acetate (3 × 50 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed to afford the partially oxidized product, aldehyde **28**, as a colorless oil (798 mg, 25%) followed by the title compound as a yellowish oil (1.70 g, 50%).

29, as a mixture of two diastereomers: ^{1}H NMR (700 MHz, $CDCl_3$) δ 1.18–1.20 (m, 3H), 1.50–1.62 (m, 3H), 1.68–1.79 (m, 2H), 1.83–1.88 (m, 1H), 1.90–2.02 (m, 2H), 2.12–2.13 (m, 1H), 2.25–2.30 (m, 1H), 2.34–2.39 (m, 1H), 2.73–2.88 (m, 2H), 3.48–3.53 (m, 1H), 3.83 (dddd, J = 14.3, 11.7, 9.0, and 3.0 Hz, 1H), 4.17–4.43 (m, 2H), 4.67 (dt, J = 9.7 and 3.5 Hz, 1H); ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 17.8, 17.9, 19.1, 19.2, 23.3, 23.4, 25.38, 25.41, 27.4, 27.5, 30.26, 30.28, 31.51, 31.54, 51.31, 51.33, 62.3, 62.4, 70.5, 70.6, 73.0, 73.1, 86.0, 86.1, 98.6, 98.9, 177.91, 177.93, 209.6, 209.7; HRMS (ESI-FTMS) m/z: [M + H][+] calcd for $C_{15}H_{23}O_5$ 283.1540; found, 283.1536.

28, as a mixture of two diastereomers: ^{1}H NMR (700 MHz, $CDCl_3$) δ 1.19 (dd, J = 7.0 and 5.8 Hz, 3H), 1.49–1.62 (m, 3H), 1.67–1.73 (m, 1H), 1.74–1.80 (m, 1H), 1.85 (qq, J = 12.0 and 3.8 Hz, 1H), 1.95 (quint, J = 7.2 Hz, 2H), 2.12 (dd, J = 3.2 and 2.3 Hz, 1H), 2.35–2.51 (m, 2H), 2.73–2.89 (m, 2H), 3.46–3.55 (m, 1H), 3.82 (dddd, J = 13.8, 11.5, 8.9, and 3.1 Hz, 1H), 4.14–4.39 (m, 2H), 4.65 (dt, J = 7.0 and 3.6 Hz, 1H), 9.73 (dd, J = 2.2 and 1.2 Hz, 1H); ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 17.7, 17.8, 19.2, 19.3, 20.5, 20.7, 25.38, 25.41, 27.4, 27.5, 30.29, 30.33, 41.3, 51.3, 51.4, 62.4, 62.5, 70.5, 70.6, 72.96, 72.98, 86.05, 86.12, 98.7, 99.0, 201.2, 201.3, 209.67, 209.70; HRMS (ESI-FTMS) m/z: [M + H][+] calcd for $C_{15}H_{23}O_4$ 267.1591; found, 267.1589.

Formation of **29** from **28** could be achieved through Pinnick oxidation as follows. The entire sample of **28** (798 mg, 3.00 mmol)

in *tert*-butanol (11.50 mL) and water (3.83 mL) at room temperature was sequentially treated with 2-methyl-2-butene (3.18 mL, 30.0 mmol), $NaH_2PO_4 \cdot H_2O$ (1.24 g, 9.00 mmol), and $NaClO_2$ (80% purity, 1.02 g, 9.00 mmol). The reaction mixture was stirred at room temperature for 20 min followed by dilution in brine (30 mL) and extraction with ethyl acetate (3 × 50 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and dried overnight under vacuum to afford **29** as a yellowish oil (853 mg, quant). Characterization by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy indicated that the sample was identical to that obtained from the above DIB-TEMPO-mediated oxidation.

Tributyl(hydroxymethyl)stannane[60]. A solution of *N,N*-diisopropylamine (21.1 mL, 150 mmol) in distilled THF (600 mL) at 0 °C was treated with *n*-BuLi solution (1.6 M in hexanes, 89.4 mL, 143 mmol). The resulting solution was stirred at 0 °C for 30 min, then tributyltin hydride (35.0 mL, 130 mmol) was added. The reaction mixture was stirred at 0 °C for 20 min followed by addition of paraformaldehyde (5.47 g, 182 mmol) and stirring at room temperature for 3 h. Upon completion, water (500 mL) was added, and the mixture was extracted with diethyl ether (3 × 200 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed [silica, short column, 100% hexanes then hexanes/ethyl acetate (5 : 1)] to yield a colorless oil (32.84 g, 79%): ^1H NMR (500 MHz, $CDCl_3$) δ 0.85–0.99 (m, 15H), 1.27–1.35 (m, 6H), 1.44–1.57 (m, 6H), 4.02 (d, J = 4.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 8.7, 13.9, 27.5, 29.3, 53.8.

Tributyl(iodomethyl)stannane[60]. A solution of *N*-iodosuccinimide (6.07 g, 27.0 mmol) in distilled THF (55.0 mL) was added dropwise to a stirred solution of Ph_3P (7.08 g, 27.0 mmol) in distilled THF (55.0 mL) at 0 °C. The resulting solution was stirred at the same temperature for 10 min followed by the addition of a solution of tributyl(hydroxymethyl)stannane in distilled THF (55.0 mL). The reaction mixture was stirred at room temperature for 16 h. Upon completion, the reaction mixture was poured into a biphasic mixture of *n*-pentane/water (150 mL/150 mL). The organic layer was collected, dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed [silica, 100% hexanes] to give a colorless oil (6.50 g, 84%): ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 9H), 0.94–1.05 (m, 6H), 1.29–1.36 (m, 6H), 1.44–1.61 (m, 6H), 1.94 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 10.8, 13.8, 27.4, 29.0.

Tributyl(methoxymethyl)stannane (Sn-Me)[54]. A solution of *N,N*-diisopropylamine (9.4 mL, 67 mmol) in distilled THF (150 mL) at −78 °C was treated with *n*-BuLi (2.5 M in hexanes, 24 mL, 60 mmol) followed by stirring at the same temperature for 30 min, then tributyltin hydride (16.2 mL, 60 mmol) was added. The reaction mixture was allowed to warm with stirring to 0 °C for 30 min, then cooled again to −78 °C and treated with methoxymethylchloride (4.6 mL, 60 mmol). The resulting mixture was allowed to warm to room temperature for 1 h, diluted with water (150 mL), and extracted with diethyl ether (3 × 150 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and purified by passage through a silica pad [hexanes/ethyl acetate (50 : 1)] to give a

colorless oil (16.89 g, 84%): ^1H NMR (500 MHz, $CDCl_3$) δ 0.84–0.98 (m, 15H), 1.26–1.34 (m, 6H), 1.43–1.56 (m, 6H), 3.29 (s, 3H), 3.69–3.72 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 9.1, 13.9, 27.5, 29.3, 63.4, 64.6.

Tributyl((methoxymethoxy)methyl)stannane (Sn-MOM)[55]. A mixture of tributyl(hydroxymethyl)stannane (6.42 g, 20.0 mmol), dimethoxymethane (53.2 mL, 600 mmol), and 4 Å molecular sieves (powdered form, 10.0 g) in CH_2Cl_2 (40 mL) was treated dropwise under stirring with $BF_3 \cdot Et_2O$ (2.72 mL, 22.0 mmol) over 2 min. The reaction mixture was stirred at room temperature for 20 h followed by filtration through a Celite pad. The Celite pad was washed thoroughly with CH_2Cl_2. The combined filtrate was shaken with saturated aqueous $NaHCO_3$ solution (100 mL). The organic layer was collected, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and purified by Kugelrohr distillation to afford a colorless oil (6.54 g, 86%): ^1H NMR (500 MHz, $CDCl_3$) δ 0.85–0.98 (m, 15H), 1.27–1.34 (m, 6H), 1.43–1.60 (m, 6H), 3.32 (s, 3H), 3.74 (s, 2H), 4.51 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 9.03, 13.85, 27.45, 29.25, 55.08, 57.75, 99.59.

***rac*-Tributyl((((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)stannane (Sn-THP)**[56]. A solution of tributyl(hydroxymethyl)stannane (6.42 g, 20.0 mmol) and 3,4-dihydropyran (3.65 mL, 40.0 mmol) in hexanes (115 mL) was stirred with Amberlyst 15 resin (4.00 g) at room temperature for 6.5 h. The reaction mixture was then filtered through a Celite pad to remove the resin. The Celite pad was thoroughly washed with hexanes. The combined filtrate was concentrated under reduced pressure and chromatographed [silica, hexanes/ethyl acetate (7 : 1)] to afford a colorless oil (7.24 g, 89%): ^1H NMR (500 MHz, $CDCl_3$) δ 0.84–0.97 (m, 15H), 1.27–1.34 (m, 6H), 1.43–1.60 (m, 10H), 1.64–1.69 (m, 1H), 1.74–1.82 (m, 1H), 3.47–3.52 (m, 1H), 3.59 (d, J = 10.6 Hz, 1H); 3.80 (ddd, J = 11.4, 8.9, and 2.7 Hz, 1H), 3.99 (d, J = 10.6 Hz, 1H), 4.39 (t, J = 3.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 9.2, 13.9, 19.4, 25.8, 27.5, 29.3, 30.8, 57.7, 61.8, 101.6.

Tributyl(methoxy(ethoxymethoxy)methyl)stannane (Sn-MEM)[57]. A solution of tributyl(hydroxymethyl)stannane (5.34 g, 16.6 mmol) in CH_2Cl_2 (17 mL) was treated with DIPEA (2.9 mL, 16.6 mmol) and then dropwise with 2-methoxyethoxymethyl chloride (2.30 mL, 19.9 mmol). The reaction mixture was stirred at room temperature overnight, followed by the addition of water (70 mL) and extraction with CH_2Cl_2 (3 × 30 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed [silica, hexanes/ethyl acetate (7 : 1)] to afford a colorless oil (4.48 g, 66%): ^1H NMR (500 MHz, $CDCl_3$) δ 0.84–0.97 (m, 15H), 1.30 (sext, J = 7.3 Hz, 6H), 1.41–1.57 (m, 6H), 3.40 (s, 3H), 3.57 (dd, J = 5.9 and 3.6 Hz, 2H), 3.65 (dd, J = 6.0 and 3.5 Hz, 2H), 3.75 (s, 2H), 4.61 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 9.0, 13.9, 27.5, 29.3, 57.9, 59.2, 66.6, 72.0, 98.7.

(Benzyloxymethyl)tributylstannane (Sn-Bn)[58]. A sample of NaH (60% in mineral oil, 120 mg, 3.0 mmol) after being washed with *n*-pentane (3 × 1.0 mL) was suspended in distilled THF (7.5 mL) under an argon atmosphere. Benzyl alcohol (270 μL, 2.6 mmol) was added dropwise. The mixture was stirred at room temperature for 1 h, treated with tributyl(iodomethyl)stannane

(862 mg, 2.0 mmol), and further stirred at room temperature for 48 h. The resulting reaction mixture was diluted in water (15 mL) and hexanes (15 mL) followed by vigorous shaking. The organic layer was collected, dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed [silica, 100% hexanes followed by hexanes/ethyl acetate (5:1)] to afford a colorless oil (647.8 mg, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85–0.98 (m, 15H), 1.26–1.34 (m, 6H), 1.44–1.58 (m, 6H), 3.75 (s, 2H), 4.42 (s, 2H), 7.24–7.35 (m, 5H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 9.1, 13.9, 27.5, 29.3, 61.6, 77.4, 127.4, 127.7, 128.3, 139.1.

Tributyl((2-(trimethylsilyl)ethoxy)methoxymethyl)stannane (Sn-SEM)[59]. A solution of tributyl(hydroxymethyl)stannane (6.42 g, 20.0 mmol) in CH_2Cl_2 (100 mL) was treated with DIPEA (17.40 mL, 100 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (4.25 mL, 24.0 mmol). The reaction mixture was stirred at reflux temperature (40 °C) with a heating mantle for 12 h followed by dilution in hexanes (500 mL). The resulting organic solution was then washed with water (2 × 200 mL) and brine (200 mL), dried (Na_2SO_4), concentrated under reduced pressure, and purified by passage through a silica pad [hexanes/ethyl acetate (30:1)] to give a colorless oil (8.38 g, 93%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 9H), 0.84–0.97 (m, 17H), 1.27–1.34 (m, 6H), 1.43–1.56 (m, 6H), 3.55–3.59 (m, 2H), 3.73–3.76 (m, 2H), 4.56 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ −1.3, 9.0, 13.9, 18.3, 27.5, 29.3, 57.7, 64.9, 98.0.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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