

Stereoselective Synthesis and Structural Confirmation of the Specialized Pro-Resolving Mediator Resolvin E4

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Cite This: *J. Org. Chem.* 2021, 86, 3535–3545



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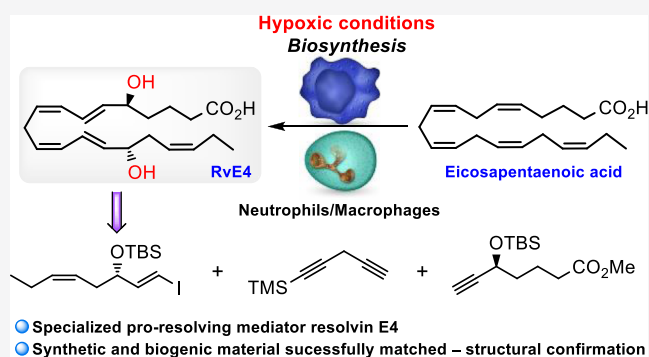


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Supporting Information

ABSTRACT: Herein, we report the stereoselective and convergent synthesis of resolvin E4, a newly identified specialized pro-resolving mediator. This synthesis proves the absolute configuration and exact olefin geometry. Key elements of the successful strategy include a highly stereoselective MacMillan organocatalytic oxyamination, a Midland Alpine borane reduction, and the use of a 1,4-pentadiyne unit as a linchpin building block. The application of reaction telescoping in several of the synthetic transformations enabled the preparation of the resolvin E4 methyl ester in 10% yield over 10 steps (longest linear sequence). The physical property (UV–Vis and LC–MS/MS) data of synthetic resolvin E4 matched those obtained from biologically produced material.



INTRODUCTION

Inflammation is a consequence of the immune system responding to injurious stimuli and constitutes an essential, protective strategy with the aim of restoring cellular homeostasis. Recent efforts concerning the mechanisms involved in the resolution of acute inflammation have provided evidence for a new superfamily of endogenous lipid mediators named specialized pro-resolving mediators (SPMs).¹ These oxygenated polyunsaturated fatty acids are biosynthesized in the presence of lipoxygenase and cyclooxygenase enzymes.² SPMs are chemically labile molecules formed in nano- to picogram amounts *in vivo*³ and exhibit anti-inflammatory and pro-resolving bioactions, often in the low nano- to picomolar range.^{2,3} Additionally, SPMs are important in the process of clearing bacterial infections and participate in host defense, organ protection, pain reduction and also play a role in tissue remodeling.³ The E-series resolvins, derived from eicosapentaenoic acid (EPA), were among the first SPMs to be reported (Figure 1).⁴

RvE1 and RvE2 have been subjected to clinical trial development programs⁵ as well as drug discovery efforts with the aim of establishing new pro-resolution agonists.⁶ The active resolution processes governed by SPMs are considered a biomedical paradigm shift.⁷

In 2019, Serhan and co-workers reported a new SPM and named it resolvin E4 (RvE4) based on its potent physiologic actions.⁸ This SPM is produced by human macrophages and neutrophils during physiologic hypoxic conditions (1–5% O₂). In contrast to the three earlier reported E-series resolvins, this SPM is formed after two consecutive lipoxygenation reactions

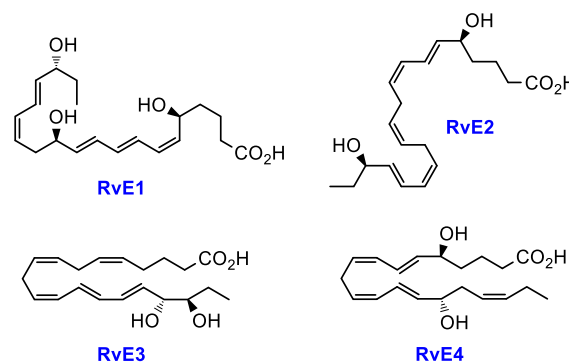
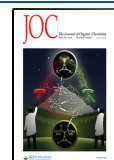


Figure 1. Reported E-series resolvins biosynthesized from EPA.

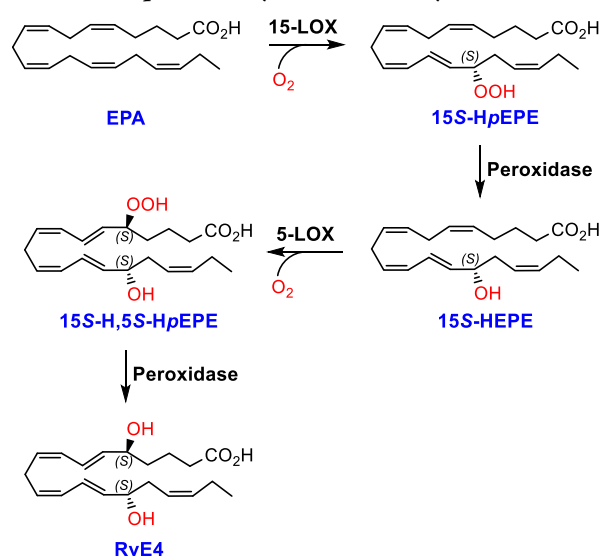
(Scheme 1).⁸ Earlier, 18S-configured epimers of RvE1, RvE2, and RvE3 have been identified.⁹ In the first step of the biosynthesis of RvE4, 15S-HpEPE is formed by 15-LOX, while the second lipoxygenation step is catalyzed by 5-LOX. Reductions of the hydroperoxide intermediates 15S-HpEPE and 5S-HpEPE are facilitated by peroxidase activity (Scheme 1).

Received: December 9, 2020

Published: February 3, 2021



Scheme 1. Proposed Biosynthetic Pathway for RvE4



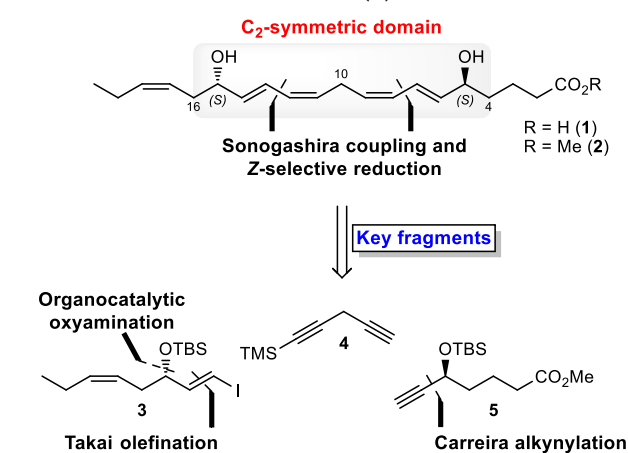
The need for absolute configuration assignments and materials of high chemical purity for further biological investigations and targeted lipidomic analyses has spurred great interest in the synthesis of the E-series resolvins.^{9a,10,11} Herein, we report the total synthesis of RvE4 (1) together with results from LC–MS/MS matching experiments that established its structure as (5S,6E,8Z,11Z,13E,15S,17Z)-5,15-dihydroxyicoso-6,8,11,13,17-pentaenoic acid.

RESULTS AND DISCUSSION

An overview of the retrosynthetic analysis applied to the tentatively assigned structure of RvE4 (1) is shown in Scheme 2. The observation of a central (Z,Z)-1,4-pentadiene structural motif contained within the C₂-symmetric C4–C16-domain of the molecule resulted in the first two disconnections being based on the Sonogashira cross-coupling reaction¹² followed by Z-selective hydrogenation. This analysis identified three key fragments 3, 5, and 1-trimethylsilyl-1,4-pentadiyne (4), the latter serving the role of a linchpin, to be convergently assembled in the synthesis.

Fragment 3 was disconnected back to *cis*-4-heptenal (6) with an enantioselective, organocatalytic oxyamination¹³ as well as a Takai olefination¹⁴ planned as the two pivotal steps in the forward direction. The Carreira alkylation was chosen as the key transformation for furnishing fragment 5, with the intent of later transforming the acetylene moiety into the corresponding *E*-vinyl halide functionality needed for the planned palladium cross-coupling chemistry.

Scheme 2. Overview of the Key Retrosynthetic Disconnections Made for RvE4 (1)



The project commenced with the construction of *ω*-3 fragment 3, starting from commercially available and affordable *cis*-4-heptenal (6). To this end, different α -oxidation protocols were first examined based on literature protocols (Table 1).

In light of these results, we settled on an enantioselective, organocatalytic α -oxyamination using 10 mol % D-proline and nitrosobenzene in CHCl₃ based on the procedure developed by the MacMillan group.^{13d} A solvent switch to ethanol preceded the NaBH₄-based reduction of the *in situ* masked aldehyde functionality, and then the comparatively weak O–N bond was cleaved using zinc and acetic acid. After this sequence, a chromatographic purification step was introduced. The overall yield obtained for the described synthetic sequence was 80%, and chiral HPLC analysis of the α -aminooxylated alcohol intermediate 21 before zinc reduction to 7 showed an enantiomeric excess of 98% (Supporting Information).

The next objective was the regioselective TBS-protection of the secondary alcohol present in the 1,2-diol system in 7, and this was achieved by first masking the primary alcohol as the corresponding bulky pivaloyl ester and then adding a catalytic amount of 4-dimethylaminopyridine (DMAP) together with an excess of TBS triflate to the reaction mixture, yielding bis-protected 8 in 81% after column chromatography. A DIBAL-H reduction then cleanly did away with the pivaloyl moiety, and the primary alcohol was obtained in a crude form after work up and removal of volatiles under high-vacuum. This material was directly subjected to a Dess–Martin oxidation¹⁵ to give the corresponding aldehyde. Passing the crude material through a short plug of silica gel to remove periodinane-related residues was found beneficial before the next reaction. Finally, the vinyl

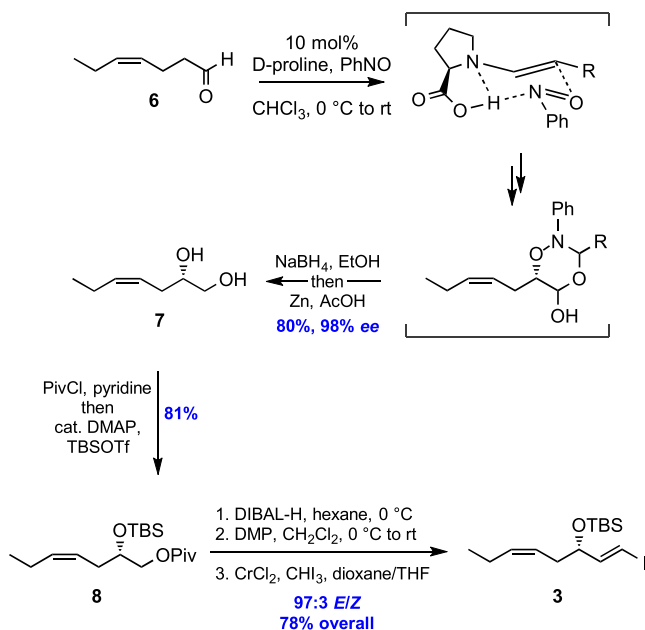
Table 1. Different Protocols Examined for the Organocatalytic Oxyamination of *cis*-4-Heptenal (6)

Catalyst	Mol%	Electrophile	Solvent	Temperature	Yield	Reference
	20		THF	25 °C	42%	13a
	2		MeCN	0 °C	20%	13b
	20		DMSO	25 °C	31%	13c
	10		CHCl ₃	0 °C	80%	13d,e

iodide portion in **3** was installed by an *E*-selective Takai olefination (>97:3, ¹H NMR analysis) with a combined yield of 78% over three steps.

The synthetic sequence depicted in Scheme 3 is shorter than our previously reported preparation¹⁶ of **3** when the step count

Scheme 3. Organocatalytic Approach to the Construction of ω -3 Fragment 3



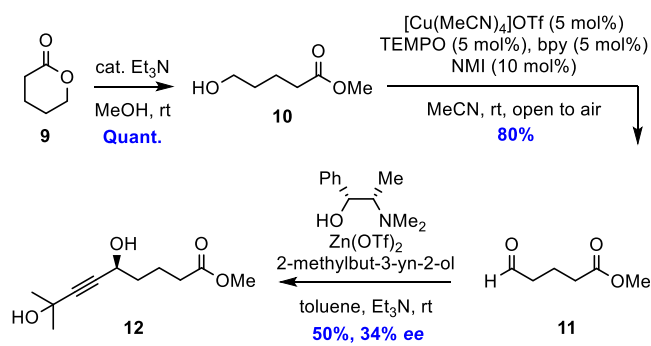
for one-pot reactions is taken into account. Furthermore, this approach comes with other benefits: for example, (i) the catalytic, highly enantioselective oxyamination replaces the rather expensive use of chiral pool starting materials of unreliable supply, (ii) the thoughtful use of reaction telescoping¹⁷ allows for the conduction of several transformations without the need to isolate, purify, and handle sensitive intermediates, and (iii) cryogenic conditions combined with an array of hazardous reagents and additives have been avoided.

Turning our attention to the preparation of α -fragment **5**, the first step was the straight-forward esterification of lactone **9** in basic methanol and a subsequent copper-catalyzed Stahl aerobic oxidation¹⁸ of the resulting primary alcohol **10**, affording **11** in good yield. The Carreira alkylation¹⁹ between aldehyde **11** and 2-methylbut-3-yn-2-ol was studied next, and we found that a yield of 50% could be achieved if a solution of the aldehyde in toluene was added dropwise with the aid of a syringe pump, over a 24 h period, to two equivalents of the corresponding alkynylzinc species of said alkyne (Scheme 4). Slow addition is often needed for α -unbranched aliphatic aldehydes in order to minimize the competing aldol self-condensation pathway.²⁰

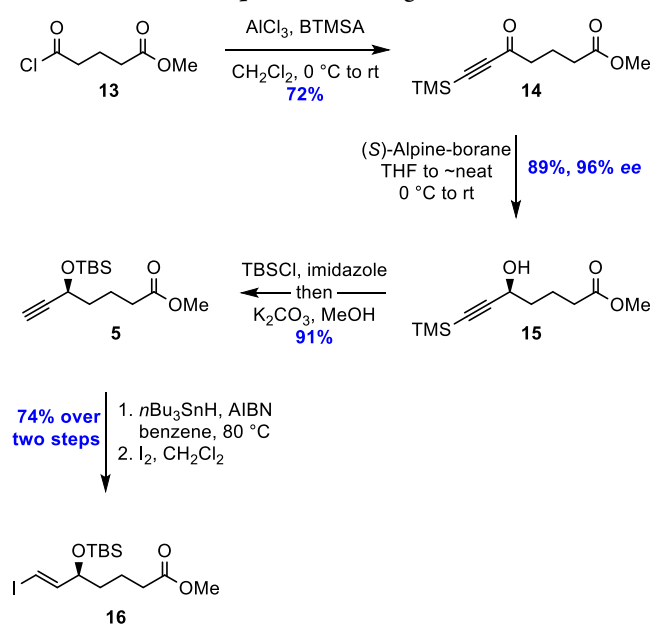
Surprisingly, however, chiral HPLC analysis of the 2-naphthoate derivative of **12** revealed that the obtained enantiomeric excess was only 34% in this case (Supporting Information), which is significantly lower than what we have previously obtained for other structurally similar substrates in hitherto unpublished work. Hence, in light of this outcome, the alkylation sequence was put to the side in favor of an alternative approach (Scheme 5).

Capitalizing on the β -silicon effect, an aliphatic Friedel–Crafts acylation between acid chloride **13** and bis-

Scheme 4. Initial Approach toward **5 Utilizing the Carreira Alkylation**



Scheme 5. Application of the Midland (*S*)-Alpine Borane Reduction in the Preparation of Fragment **16**



(trimethylsilyl)acetylene in the presence of Lewis acidic $AlCl_3$, gave ketone **14** in 72% yield.²¹ Gram-scale asymmetric reduction of the alkynyl ketone was achieved by the addition of the Midland (*S*)-Alpine borane reagent²² in tetrahydrofuran (THF) at $0^\circ C$, followed by swift removal of the solvent to give essentially neat conditions, ultimately furnishing the desired propargylic alcohol **15** in 96% enantiomeric excess and 89% yield after workup and purification (Supporting Information). The secondary alcohol in **15** was then protected using TBS chloride and imidazole in dichloromethane, followed by a solvent switch to methanol and addition of K_2CO_3 , effectively removing the TMS-group attached to alkyne **5** in 91% overall yield.

At this stage, it was necessary to convert the terminal acetylene into the corresponding *E*-vinyl iodide, and this was achieved by a two-step process: first, free radical hydrostannylation was initiated using a catalytic amount of azobisisobutyronitrile (AIBN), with excess tributyltin hydride added to ensure complete equilibration to the desired geometrical isomer, and then, iododestannylation was performed, yielding **16** in 74% over two steps.

The first of the two planned Sonogashira cross-coupling reactions was performed using catalytic amounts of Pd-

(PPh₃)₂Cl₂/CuI, which cleanly effected the union between vinyl iodide **16** and linchpin **4** in 98% yield. Given the inherent lability of the resulting diyne system in **17**, especially to basic reaction conditions, protodesilylation was performed in a mild manner by the employment of AgNO₃ and KCN,²³ affording the terminal alkyne **18** in 65% yield.

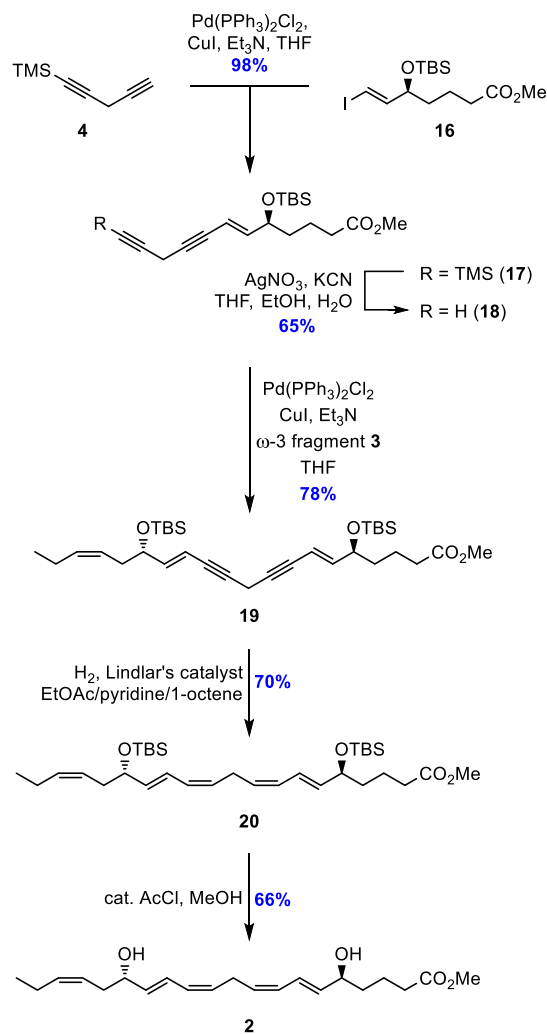
The same catalyst system was then used again for the final Sonogashira carbon–carbon bond-forming reaction between alkyne **18** and vinyl iodide **3**, giving the complete carbon skeleton **19** in 78%. The two internal, conjugated triple bonds were reduced in 70% yield using the *tried-and-tested* Lindlar hydrogenation protocol which involves the utilization of a mixed solvent system consisting of EtOAc/pyridine/1-octene.²⁴ The inclusion of pyridine helps to modulate and control the activity of the heterogeneous catalyst, and 1-octene serves as a sacrificial olefin, the presence of which aids in minimizing competing over-reduction as the reaction nears completion. Removal of the two TBS-groups in **20** was first attempted using tetra-*n*-butylammonium fluoride (TBAF) in THF; however, significant byproduct formation was observed, leading to a diminished yield and difficulties during the purification process. A different deprotection approach was thus sought and found. Subjecting **20** instead to a catalytic amount of acetic chloride in methanol²⁵ afforded RvE4 methyl ester (**2**) in 66% yield (Scheme 6) and chemical purity >97% (Supporting Information). The NMR- (¹H, ¹³C, and COSY), MS-, and UV-data were all in accordance with the structure of **2** (Supporting Information).

MRM LC–MS/MS Matching Experiments. Since SPMs are formed in the nano- to picogram range *in vivo*, direct NMR analyses for structural verification are not viable. In order to ascertain that our synthetically prepared material was identical to that of authentic RvE4 (**1**) produced *in vitro*, matching experiments were conducted. Due to the chemically sensitive nature of this and other SPMs,²⁶ hydrolysis was performed just prior to the LC–MS/MS experiments, as earlier reported.⁸ In Figure 2, top panel, the targeted MRM chromatogram from biogenic RvE4 (**1**) is shown together with an MS/MS spectrum displaying the molecular ion at *m/z* 333 (*M* – *H*) as well as the accompanying daughter ions (*m/z* 315 (*M* – *H* – H₂O), *m/z* 271 (*M* – *H* – H₂O – CO₂), *m/z* 253 (*M* – *H* – 2H₂O – CO₂), *m/z* 235, *m/z* 217 (235 – H₂O), *m/z* 199 (217 – H₂O), *m/z* 191 (235 – CO₂), and *m/z* 173 (235 – H₂O – CO₂) and *m/z* 115). In the middle panel, the chromatographic behavior of synthetically produced RvE4 (**1**), with an identical observed retention time (12.9 min) to that of the authentic material, is shown. Next, the result from coinjection of the biologically produced material and synthetically produced RvE4 (**1**) appears in the bottom panel, resulting in both coelution as well as an overall matching MS/MS fragmentation fingerprint. Additionally, the UV–Vis spectrum was in agreement with the original isolation of RvE4 (**1**).⁸ Overall, these results confirm that the synthetic material matched the biogenic material.

CONCLUSIONS

A total synthesis providing multi-milligram quantities of the methyl ester **2** of the SPM RvE4 (**1**) has been reported in 10% yield over 10 steps (longest linear sequence). Several of the reactions were performed using telescoping techniques, establishing the basis for an efficient total synthesis. Moreover, the successful use of the organocatalytic MacMillian oxyamination reaction is presented. The application of stereo-

Scheme 6. Sonogashira Cross-Coupling Reactions and Z-Selective Hydrogenation to Complete the Synthesis of RvE4 Methyl Ester (**2**)



selective organocatalytic protocols offers many advantages in the total synthesis of natural products.²⁷ The integrity of the synthetically prepared material was demonstrated through matching experiments with authentic material obtained from human macrophages and neutrophils during hypoxic conditions. These results showed that synthetic and biologically produced RvE4 (**1**) matched, thus establishing both the absolute configurations of the carbinol atoms as well as an overall alkene geometry. Collectively, this provided evidence for the complete stereochemical assignment as (5*S*,6*E*,8*Z*,11-*Z*,13*E*,15*S*,17*Z*)-5,15-dihydroxyicosa-6,8,11,13,17-pentaenoic acid.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all commercially available reagents and solvents were used in the form they were supplied without any further purification. The stated yields are based on the isolated material. All sensitive reactions were performed under an argon or nitrogen atmosphere using Schlenk techniques. Reaction flasks were covered with aluminum foil during sensitive reactions and storage to minimize exposure to light. Thin layer chromatography was performed on silica gel 60 F₂₅₄ aluminum-backed plates fabricated by Merck. Flash column chromatography was performed on silica gel 60 (40–63 μm) produced by Merck. NMR spectra were recorded on a

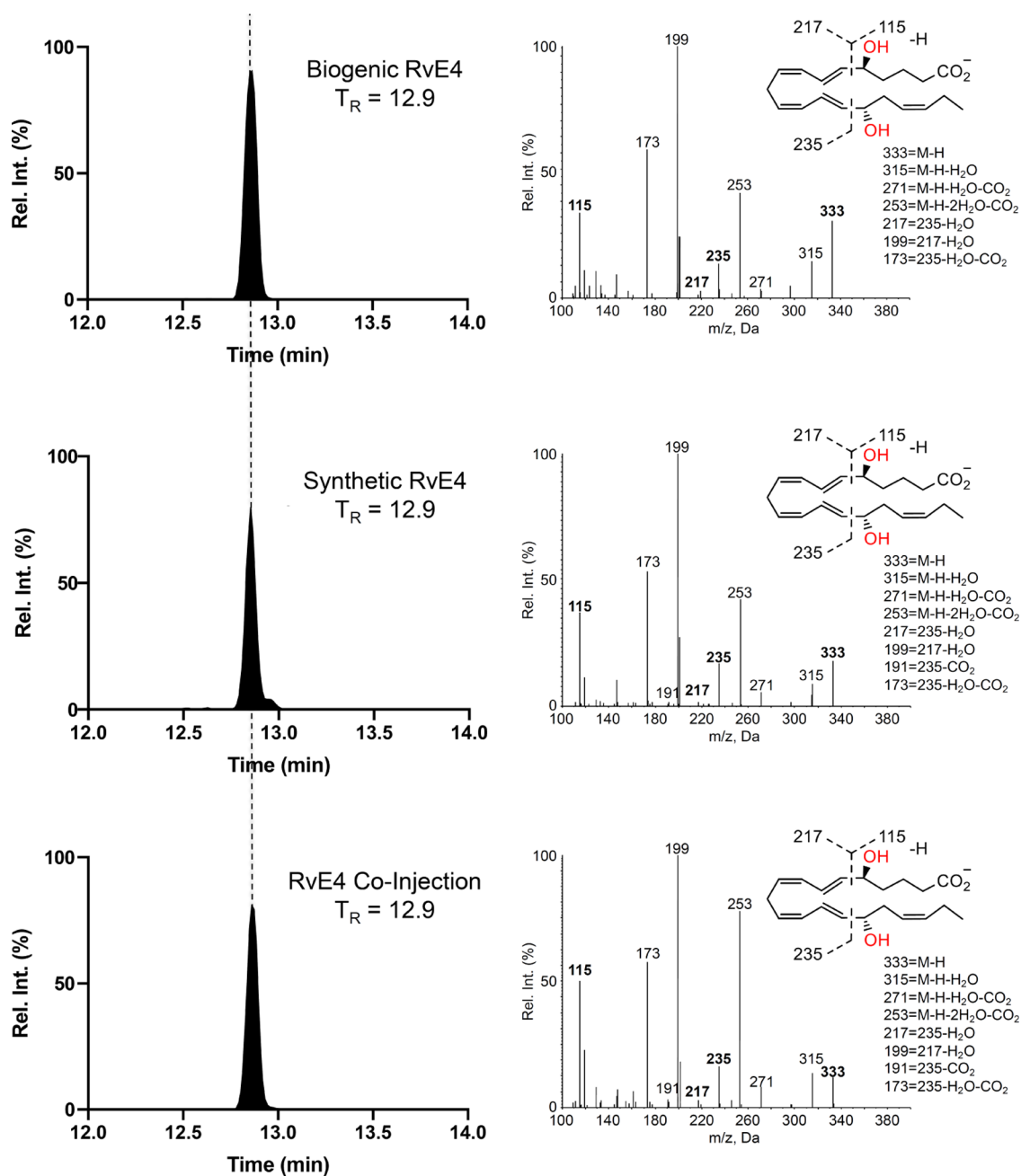


Figure 2. MRM chromatograms and MS/MS spectra obtained from the matching experiments.

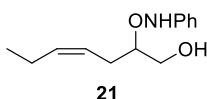
Bruker AVII400 or Bruker DPX300 spectrometer at 400 or 300 MHz, respectively for ^1H NMR and at 101 or 75 MHz, respectively for ^{13}C NMR. Coupling constants (J) are reported in hertz, and chemical shifts are reported in parts per million (δ) relative to the central residual protium solvent resonance in ^1H NMR ($\text{CDCl}_3 = \delta$ 7.26, $\text{DMSO}-d_6 = \delta$ 2.50 and $\text{MeOD} = \delta$ 3.31) and the central carbon solvent resonance in ^{13}C NMR ($\text{CDCl}_3 = \delta$ 77.00 ppm, $\text{DMSO}-d_6 = \delta$ 39.43 and $\text{MeOD} = \delta$ 49.00). Optical rotations were measured using a PerkinElmer 341 polarimeter. Mass spectra were recorded at 70 eV on a Micromass Prospec Q or Micromass QTOF 2 W spectrometer using ESI as the method of ionization. High-resolution mass spectra were recorded at 70 eV on a Micromass Prospec Q or Micromass QTOF 2W spectrometer using ESI as the method of ionization. HPLC-analyses were performed using an AD-H stationary phase (CHIR-ALPAK, 4.6×250 mm, particle size $5 \mu\text{m}$, from Diacel Corporation) or a C_{18} stationary phase (Eclipse XDBC $_{18}$, 4.6×250 mm, particle size $5 \mu\text{m}$, from Agilent Technologies), applying the conditions stated.

The UV–Vis spectrum was recorded using an Agilent Technologies Cary 8485 UV–Vis spectrophotometer using quartz cuvettes.

(+)-(S,Z)-Hept-4-ene-1,2-Diol (7). Diol 7 was prepared according to the literature with minor adjustments.^{13d,e} Nitrosobenzene (536 mg, 5.00 mmol, 1.00 equiv) and D-proline (58.0 mg, 0.500 mmol, 10.0 mol %) were dissolved in CHCl_3 (2.5 mL) and cooled to 0 °C. *cis*-4-Heptenal (6, 1.98 mL, 1.68 g, 15.0 mmol, 3.00 equiv) was added dropwise, and the reaction was stirred at 0 °C for 2 h. The reaction mixture was then added dropwise to a solution of NaBH_4 (567 mg, 15.0 mmol, 3.00 equiv) in EtOH (30 mL) at 0 °C and stirred at this temperature for an additional 2 h. The solvent was removed *in vacuo* and to the product was added sat. aq. NaHCO_3 (10 mL) followed by extraction with EtOAc (3×10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The product was dissolved in EtOH/AcOH (3:1, 28.0 mL), and zinc powder (3.27 g, 50.0 mmol, 10.0 equiv) was added. The reaction mixture was stirred at room temperature overnight, filtrated through Celite, and concentrated *in vacuo*. The material thus obtained was

purified by flash column chromatography (SiO₂, gradient elution, 50–70% EtOAc in hexane) to give the desired diol **7** (522 mg, 4.01 mmol, 80%) as a clear oil. *R*_f (50% EtOAc in hexane, visualized by KMnO₄-stain) = 0.32; [α]_D²⁵ = +9.5 (*c* 1.0, CHCl₃) [Lit.²⁸ [α]_D²⁵ = +9.0 (*c* 1.0, CHCl₃)]; ¹H NMR (400 MHz, MeOD): δ 5.55–5.35 (m, 2H), 3.67–3.55 (m, 1H), 3.50 (dd, *J* = 11.1, 4.3 Hz, 1H), 3.42 (dd, *J* = 11.1, 6.5 Hz, 1H), 2.35–2.23 (m, 1H), 2.22–2.12 (m, 1H), 2.08 (p, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H); ¹³C{¹H} NMR (101 MHz, MeOD): δ 134.6, 125.8, 73.4, 66.8, 32.3, 21.6, 14.6; HRESIMS *m/z*: 153.0885 [M + Na]⁺ (calcd for C₇H₁₄O₂Na, 153.0886).

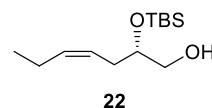
A small amount of the α -aminoxylated alcohol intermediate was kept for HPLC analysis. The enantiomeric excess (98%) was determined by HPLC analysis using a chiral column (AD-H, *i*-PrOH/hexane, 5:95, 1.0 mL/min): *t*_r(major) = 19.54 min, *t*_r(minor) = 26.13 min.



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(Z)-2-((Phenylamino)oxy)hept-4-en-1-ol (21). Nitrosobenzene (96.0 mg, 0.884 mmol, 1.00 equiv) and DL-proline (10.4 mg, 88.4 μ mol, 10.0 mol %) were dissolved in CHCl₃ (0.45 mL) and cooled to 0 °C. *cis*-4-Heptenal (**6**, 0.354 mL, 300 mg, 2.65 mmol, 3.00 equiv) was added dropwise, and the reaction was stirred at 0 °C for 2 h. The reaction mixture was added dropwise to a solution of NaBH₄ (102 mg, 2.65 mmol, 3.00 equiv) in EtOH (5.4 mL) at 0 °C and stirred at the same temperature for an additional 2 h. The solvent was removed *in vacuo*, and to the crude product was added sat. aq. NaHCO₃ (1.8 mL) followed by extraction with EtOAc (3 \times 2 mL) and the combined organic phase was dried (Na₂SO₄), filtrated and concentrated *in vacuo*. The crude product thus obtained was filtrated through a short plug of silica gel (50% EtOAc in hexane) to yield the desired α -aminoxylated alcohol intermediate **21** (176 mg, 0.796 mmol, 90%) as a yellow oil. *R*_f (20% EtOAc in hexane, visualized by UV and KMnO₄ stain) = 0.28; ¹H NMR (400 MHz, CDCl₃): δ 7.38–7.26 (m, 3H), 7.05–7.01 (m, 2H), 5.63–5.51 (m, 1H), 5.48–5.38 (m, 1H), 4.10–3.96 (m, 1H), 3.88 (dd, *J* = 12.1, 2.8 Hz, 1H), 3.79 (dd, *J* = 12.1, 6.5 Hz, 1H), 2.50 (app dt, *J* = 13.7, 6.6 Hz, 1H), 2.37 (app dt, *J* = 14.7, 7.5 Hz, 1H), 2.10 (p, *J* = 7.3 Hz, 1H), 1.00 (t, *J* = 7.5 Hz, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 148.5, 134.7, 129.2 (2C), 123.8, 122.7, 115.0 (2C), 84.0, 64.9, 28.1, 20.8, 14.3; HRESIMS *m/z*: 244.1306 [M + Na]⁺ (calcd for C₁₃H₁₉NO₂Na, 244.1308).

(S,Z)-2-((tert-Butyldimethylsilyl)oxy)hept-4-en-1-yl Pivalate (8). Diol **7** (200 mg, 1.54 mmol, 1.00 equiv) was dissolved in a 1:1 mixture of CH₂Cl₂/pyridine (4.6 mL) and cooled to 0 °C. Then, trimethylacetyl chloride (0.227 mL, 1.85 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 0 °C until deemed complete by TLC (30% EtOAc in hexane, ~2 h). TBSTf (0.88 mL, 3.83 mmol, 2.50 equiv) was then added dropwise followed by addition of one crystal of DMAP. Stirring was continued at 0 °C until deemed complete by TLC (30% EtOAc in hexane, ~2 h). The reaction mixture was quenched with sat. aq. NaHCO₃ (10 mL), extracted with EtOAc (3 \times 5 mL), dried (Na₂SO₄), filtrated, and concentrated *in vacuo*. The crude product thus obtained was purified by flash chromatography (SiO₂, 2% EtOAc in hexane) to yield **8** (409 mg, 1.25 mmol, 81%) as a clear oil. *R*_f (3.5% EtOAc in hexane, visualized by KMnO₄-stain) = 0.29; [α]_D²⁵ = +7.0 (*c* 0.1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ 5.53–5.43 (m, 1H), 5.40–5.33 (m, 1H), 3.99 (dd, *J* = 11.0, 5.2 Hz, 1H), 3.93 (dd, *J* = 11.0, 5.3 Hz, 1H), 3.87 (p, *J* = 5.6 Hz, 1H), 2.36–2.17 (m, 2H), 2.04 (p, *J* = 7.5 Hz, 2H), 1.21 (s, 9H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.88 (s, 9H), 0.08–0.07 (2 \times s, 6H); ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 178.6, 134.2, 124.1, 70.3, 67.8, 38.9, 32.6, 27.4 (3C), 25.9 (3C), 20.8, 18.2, 14.3, –4.5, –4.5; HRESIMS *m/z*: 351.2325 [M + Na]⁺ (calcd for C₁₈H₃₆O₃SiNa, 351.2326).



22

(S,Z)-2-((tert-Butyldimethylsilyl)oxy)hept-4-en-1-ol (22). The pivalate **8** (674 mg, 2.05 mmol, 1.00 equiv) was dissolved in hexane (4.8 mL) and cooled to 0 °C. DIBAL-H (1.0 M in hexane, 5.13 mL, 5.13 mmol, 2.50 equiv) was added dropwise, and the reaction mixture was stirred until deemed complete by TLC (20% EtOAc in hexane, ~2 h). MeOH (2.7 mL) was added to quench the reaction followed by addition of sat. aq. potassium sodium tartrate (27 mL). The aqueous phase was extracted with Et₂O (3 \times 7 mL). The combined organic phase was dried (Na₂SO₄), filtrated, concentrated *in vacuo*, and then kept under high vacuum for 2 h. The resulting alcohol intermediate was used without further purification in the next step. *R*_f (20% EtOAc in hexane, visualized by KMnO₄-stain) = 0.48; [α]_D²⁵ = +19.8 (*c* 0.1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ 5.53–5.40 (m, 1H), 5.39–5.25 (m, 1H), 3.79–3.71 (m, 1H), 3.56 (dd, *J* = 11.0, 3.6 Hz, 1H), 3.44 (dd, *J* = 11.0, 5.5 Hz, 1H), 2.35–2.17 (m, 2H), 2.05 (p, *J* = 7.4 Hz, 2H), 1.86–1.73 (br s, 1H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 134.3, 124.2, 72.9, 66.1, 32.1, 26.0 (3C), 20.8, 18.2, 14.3, –4.3, –4.5; HRESIMS *m/z*: 267.1751 [M + Na]⁺ (calcd for C₁₃H₂₈O₂SiNa, 267.1751).

tert-Butyl(((S,1E,5Z)-1-iodoocta-1,5-dien-3-yl)oxy)dimethylsilane (3). Alcohol **22** was dissolved in CH₂Cl₂ (60 mL) and cooled to 0 °C. The Dess–Martin periodinane reagent (1.04 g, 2.45 mmol, 1.20 equiv) was then added in one portion. The reaction mixture was removed from the cooling bath, and stirring was continued for 4 h. The reaction was quenched by addition of sat. aq. Na₂S₂O₃ (13 mL), and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (2 \times 15 mL). The combined organic phase was dried (Na₂SO₄), filtrated, and concentrated *in vacuo*. The crude product thus obtained was filtrated through a short plug of silica gel (10% EtOAc in hexane, *R*_f (10% EtOAc in hexane) = 0.52) to remove the leftover and spent DMP-reagent and then concentrated *in vacuo*.

A 50 mL flask was charged with CrCl₂ (2.02 g, 16.4 mmol, 8.00 equiv), and the salt was dried under high-vacuum using a heat gun, cooled to ambient temperature, and covered with aluminum foil. Dry THF (2.8 mL) and dry dioxane (16 mL) were added, and the resulting suspension was cooled to 0 °C before CHI₃ (2.03 g, 5.13 mmol, 2.50 equiv) was added. The reaction mixture was stirred at room temperature for 2 h, at which point the mixture turned from dark-green to red-brown. The reaction mixture was cooled to 0 °C, and the aldehyde dissolved in dry dioxane (2.0 mL) was added in a dropwise manner, and the reaction mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of sat. aq. NH₄Cl (10 mL). The aqueous phase was extracted with Et₂O (3 \times 7 mL). The combined organic phase was washed successively with sat. aq. Na₂S₂O₃ (~2 mL) and brine, dried (Na₂SO₄), filtrated, and concentrated *in vacuo*. The crude product thus obtained was purified by flash chromatography (SiO₂, gradient elution, 0–1% EtOAc in hexane) to yield vinyl iodide **3** (586 mg, 1.60 mmol, 78% from **8**, *E/Z* = 97:3) as a pale yellow oil. *R*_f (1% EtOAc in hexane, visualized by UV and KMnO₄ stain) = 0.50; [α]_D²⁰ = –4.1 (*c* 0.3, benzene); ¹H NMR (400 MHz, CDCl₃): δ 6.54 (dd, *J* = 14.3, 5.7 Hz, 1H), 6.21 (dd, *J* = 14.4, 1.3 Hz, 1H), 5.53–5.43 (m, 1H), 5.38–5.24 (m, 1H), 4.16–3.99 (m, 1H), 2.29–2.17 (m, 2H), 2.08–1.97 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 148.9, 134.4, 123.8, 75.9, 75.2, 35.7, 26.0 (3C), 20.9, 18.4, 14.4, –4.5, –4.7; HRESIMS *m/z*: 389.0768 [M + Na]⁺ (calcd for C₁₄H₂₇IOSiNa, 389.0768).

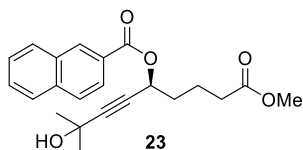
Methyl 5-Hydroxypentanoate (10). To a solution of δ -valerolactone (**9**, 5.0 g, 50 mmol, 1.0 equiv) in MeOH (50 mL) was added triethylamine (2.4 mL, 17 mmol, 34 mol %). The reaction was stirred for 18 h at room temperature. The reaction mixture was then filtrated through a short plug of silica gel, and the plug was washed with additional MeOH and concentrated *in vacuo* to yield the desired methyl ester **10** (6.6 g, 50 mmol, quant.) as a clear oil. The product was used as is in the next reaction. The spectroscopic data

was in agreement with previously reported data.²⁹ ¹H NMR (400 MHz, DMSO-*d*₆): δ 4.38 (t, *J* = 5.2 Hz, 1H), 3.58 (s, 3H), 3.38 (app td, *J* = 6.4, 5.2 Hz, 2H), 2.30 (t, *J* = 7.4 Hz, 2H), 1.70–1.47 (m, 2H), 1.46–1.32 (m, 2H); ¹³C{¹H} NMR (101 MHz, DMSO): δ 173.4, 60.2, 51.2, 33.1, 31.8, 21.2.

Methyl 5-Oxopentanoate (11). Alcohol **10** (200 mg, 1.51 mmol, 1.00 equiv) was dissolved in MeCN (15 mL). [Cu(MeCN)₄]-OTf (28.3 mg, 75.1 μmol, 5.00 mol %) and commercial Stahl aerobic oxidation TEMPO solution (0.47 mL) were added, and the reaction was stirred open to air until complete as deemed by TLC. The reaction mixture was diluted with Et₂O (15 mL) and filtrated through a short plug of silica gel. The plug was washed with additional Et₂O. The solvent was removed *in vacuo*, and the crude product thus obtained was purified by flash column chromatography (SiO₂, 16% EtOAc in hexane) to yield the desired aldehyde **11** (158 mg, 1.21 mmol, 80%) as a clear oil. The spectroscopic data was in agreement with previously reported data.³⁰ *R*_f (14% EtOAc in hexane, visualized by KMnO₄-stain) = 0.15; ¹H NMR (400 MHz, CDCl₃): δ 9.77 (t, *J* = 1.3 Hz, 1H), 3.67 (s, 3H), 2.53 (td, *J* = 7.2, 1.3 Hz, 2H), 2.37 (t, *J* = 7.2 Hz, 2H), 1.95 (p, *J* = 7.2 Hz, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 201.6, 173.5, 51.8, 43.0, 33.1, 17.5.

Methyl (S)-5-((tert-Butyldimethylsilyloxy)-8-hydroxy-8-methylnon-6-ynoate (12). Zn(OTf)₂ (559 mg, 1.54 mmol, 2.00 equiv) was added to a flame-dried flask under argon and dried under high vacuum at 120 °C overnight. The flask was cooled and vented with argon, before (1*R*, 2*S*)-(-)-*N*-methylephedrine (289 mg, 1.61 mmol, 2.10 equiv) was added. The flask was purged with argon (~15 min), and then, toluene (1.3 mL) and triethylamine (225 μL, 1.61 mmol, 2.10 equiv) were added. The reaction mixture was stirred for 2 h followed by the addition of 2-methyl-3-butyne-2-ol (149 μL, 1.54 mmol, 2.00 equiv). The content of the flask was stirred for 20 min before starting the addition of aldehyde **11** (100 mg, 0.768 mmol, 1.00 equiv), dissolved in toluene (1.8 mL) using a syringe pump over 24 h. The reaction was quenched by the addition of sat. aq. NH₄Cl (~5 mL) and extracted with ether (5 × 5 mL). The organic phase was dried (Na₂SO₄), filtrated, and concentrated *in vacuo*. The material thus obtained was purified by flash chromatography (SiO₂, 50% EtOAc in hexane), yielding diol **12** (82.3 mg, 0.384 mmol, 50%) as a clear oil. *R*_f (50% EtOAc in hexane, visualized by KMnO₄-stain) = 0.13; [α]_D²⁵ = -0.9 (c 1.0, MeOH); ¹H NMR (400 MHz, MeOD): δ 4.33 (t, *J* = 6.4 Hz, 1H), 3.66 (s, 3H), 2.37 (t, *J* = 7.3 Hz, 2H), 1.81–1.72 (m, 2H), 1.71–1.61 (m, 2H), 1.46 (s, 6H); ¹³C{¹H} NMR (101 MHz, MeOD): δ 175.7, 90.3, 83.6, 65.4, 62.4, 52.0, 49.4, 38.2, 34.4, 31.7, 21.9; HRESIMS *m/z*: 237.1098 [M + Na]⁺ (calcd for C₁₁H₁₈O₄Na, 237.1097).

Methyl 5,8-Dihydroxy-8-methylnon-6-ynoate (rac-12). 2-Methyl-3-butyne-2-ol (74.5 μL, 0.786 mmol, 1.00 equiv) in THF (34 mL) was cooled to -78 °C. *n*BuLi (1.6 M in hexane, 0.983 mL, 1.57 mmol, 2.00 equiv) was added dropwise over 15 min. The reaction mixture was stirred for 30 min before aldehyde **11** (100 mg, 0.768 mmol, 1.00 equiv) in THF (1.74 mL) was added dropwise. After 2 h at -78 °C, the reaction was quenched by addition of sat. aq. NH₄Cl (7 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phase was dried (Na₂SO₄), filtrated, and concentrated *in vacuo*. The material thus obtained was purified by flash chromatography (SiO₂, 50% EtOAc in hexane), yielding diol **rac-12** (62.0 mg, 0.289 mmol, 37%) as a clear oil. The obtained experimental data matched that given for compound **12**.



(S)-7-Methoxy-7-oxo-1-(trimethylsilyl)hept-1-yn-3-yl 2-Naphthoate (23). Propargylic alcohol **12** (20.0 mg, 93.3 μmol, 1.00 equiv) was dissolved in CH₂Cl₂ (0.43 mL) and cooled to 0 °C. Triethylamine (39.0 μL, 0.280 mmol, 3.00 equiv) was added followed by DMAP (1.10 mg, 9.00 μmol, 10.0 mol %). Next, 2-naphthoyl chloride (21.4 mg, 0.112 mmol, 1.20 equiv) was added in one portion.

The reaction mixture was allowed to warm up to room temperature and stirred overnight. The solvent was removed under a gentle stream of argon, and the material thus obtained was purified by flash column chromatography (SiO₂, gradient elution, 10–30% EtOAc in hexane) to give the desired naphthalate **23** (31.5 mg, 85.6 μmol, 92%) as a white solid. The enantiomeric excess (34%) was determined by HPLC analysis using a chiral column (AD-H, *i*-PrOH/hexane, 15:85, 1.0 mL/min): *t*_r(major) = 17.44 min, *t*_r(minor) = 21.99 min. *R*_f (30% EtOAc in hexane, visualized by UV and KMnO₄ stain) = 0.18; [α]_D²⁵ = +10.5 (c 0.6, CHCl₃); ¹H NMR (300 MHz, MeOD): δ 8.61 (s, 1H), 8.13–7.80 (m, 4H), 7.61 (p, *J* = 7.1 Hz, 2H), 5.72 (t, *J* = 5.8 Hz, 1H), 3.66 (s, 3H), 2.46 (t, *J* = 6.6 Hz, 2H), 1.93 (m, 4H), 1.47 (s, 6H); ¹³C{¹H} NMR (101 MHz, MeOD): δ 175.4, 166.9, 137.1, 133.9, 132.2, 130.4, 129.7, 129.4, 128.9, 128.3, 128.0, 126.0, 92.2, 79.7, 65.6, 65.4, 52.1, 35.3, 34.1, 31.6, 21.7 (2C); HRESIMS *m/z*: 391.1516 [M + Na]⁺ (calcd for C₂₂H₂₄O₅Na, 391.1516).

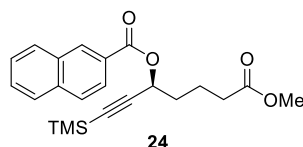
The exact same procedure was followed for the preparation of racemic naphthalate. Yield: 30.8 mg, 0.0837 mmol, 90%. The obtained experimental data matched that given for compound **23**.

Methyl 5-Oxo-7-(trimethylsilyl)hept-6-ynoate (14). A flame-dried flask under argon was charged with AlCl₃ (10.5 g, 78.8 mmol, 1.30 equiv) and CH₂Cl₂ (75 mL) at 0 °C. A solution of bis(trimethylsilyl)acetylene (10.4 g, 60.8 mmol, 1.00 equiv) and methyl 4-(chloroformyl)butyrate (**13**, 10.0 g, 60.8 mmol, 1.00 equiv) in CH₂Cl₂ (75 mL) was then added in a dropwise manner over 15 min. The reaction mixture was stirred at 0 °C for 30 min, warmed up to room temperature over a period of 45 min, and then cooled back down to 0 °C. The reaction was quenched by the addition of 1 M HCl (80 mL) and stirred for 10 min. The resulting thick suspension was vacuum filtrated through a short plug of silica gel directly into a separatory funnel, and the plug was washed with additional fresh CH₂Cl₂ (50 mL). The phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phase was dried (Na₂SO₄), filtrated, and concentrated *in vacuo*. The crude product thus obtained was purified by flash column chromatography (SiO₂, 10% EtOAc in hexane) to yield the desired product **14** (9.90 g, 43.7 mmol 72%) as a yellow oil. The spectroscopic data was in agreement with previously reported data.³¹ *R*_f (10% EtOAc in hexane, visualized by KMnO₄-stain) = 0.27; ¹H NMR (400 MHz, CDCl₃): δ 3.68 (s, 3H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.37 (t, *J* = 7.3 Hz, 2H), 1.97 (p, *J* = 7.3 Hz, 2H), 0.24 (s, 9H); ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 186.8, 173.5, 101.9, 98.3, 51.8, 44.3, 32.9, 19.1, -0.6 (3C); HRESIMS *m/z*: 249.0917 [M + Na]⁺ (calcd for C₁₁H₁₈O₃SiNa, 249.0917).

Methyl (S)-5-Hydroxy-7-(trimethylsilyl)hept-6-ynoate (15). Ketone **14** (5.66 g, 25.0 mmol, 1.00 equiv) was azeotropically dried with 2-MeTHF (2 × 15 mL) and then placed under high vacuum for 30 min. The flask was vented with argon and cooled to -10 °C, and (S)-Alpine-borane solution (0.5 M in THF, 100 mL, 50.0 mmol, 2.00 equiv) was added over a period of 15 min. Most of the THF solvent was immediately removed under vacuum with efficient stirring while warming up to 0 °C. The resulting, highly viscous reaction mixture was then allowed to warm to room temperature and stirred overnight. Next, the reaction mixture was cooled to 0 °C, and acetaldehyde (1.40 mL, 1.10 g, 25.0 mmol, 1.00 equiv) was added in a dropwise manner. After 15 min, diethyl ether (100 mL) was added, followed by the dropwise addition of ethanolamine (3.00 mL, 3.00 g, 50.0 mmol, 2.00 equiv). The reaction mixture was stirred for 30 min at 0 °C, warmed to room temperature, and then stirred an additional hour. The white, solid 9-BBN-ethanolamine complex was removed by filtration, and the filtrate was washed with water (2 × 30 mL). The organic phase was dried (Na₂SO₄), filtrated, and concentrated *in vacuo*. The crude product thus obtained was purified by flash column chromatography (SiO₂, gradient elution, 10–20% EtOAc in hexane) to give the desired product **15** (5.10 g, 22.3 mmol, 89%) as a clear oil. *R*_f (20% EtOAc in hexane, visualized by KMnO₄-stain) = 0.21; [α]_D²⁰ = -1.0 (c 1.0, CHCl₃) [Lit.³² [α]_D²¹ = -0.7 (c 1.1, CHCl₃)]; ¹H NMR (400 MHz, CDCl₃): δ 4.37 (t, *J* = 6.2 Hz, 1H), 3.67 (s, 3H), 2.38 (t, *J* = 7.1 Hz, 2H), 1.91 (s, 1H), 1.85–1.68 (m, 4H), 0.16 (s, 9H); ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 174.0, 106.5, 89.8, 62.5, 51.7, 37.0, 33.7, 20.7,

0.0 (3C); HRESIMS m/z : 251.1073 $[M + Na]^+$ (calcd for $C_{11}H_{20}O_3SiNa$, 251.1074).

Methyl 5-Hydroxy-7-(trimethylsilyl)hept-6-ynoate (rac-15). Ketone **14** (200 mg, 0.884 mmol, 1.00 equiv) was azeotropically dried with 2-MeTHF (2×1 mL) and then placed under high vacuum for 30 min. The flask was cooled to 0°C , and 9-BBN-H (0.5 M in THF, 3.53 mL, 1.77 mmol, 2.00 equiv) was added, and approximately half the solvent volume was removed under vacuum at room temperature. The reaction mixture was stirred for 72 h before acetaldehyde (0.05 mL, 0.884 mmol, 1.00 equiv) was added dropwise, and the reaction mixture was stirred for an additional hour. The reaction mixture was diluted with Et_2O (5 mL), and ethanolamine (53.0 μL , 0.884 mmol, 1.00 equiv) was added in a dropwise manner. After 30 min, the reaction mixture was concentrated *in vacuo* to give a yellow oil together with some solid material. Water (5 mL) was added, and the aqueous phase was extracted with Et_2O (3×3 mL). The organic phase was dried (Na_2SO_4), filtrated, and concentrated *in vacuo*. The crude material thus obtained was purified by flash column chromatography (SiO_2 , gradient elution, 10–20% EtOAc in hexane) to give the desired racemic product **rac-15** (109 mg, 0.477 mmol, 54%) as a clear oil. The obtained experimental data matched that given for compound **15**.



(S)-7-Methoxy-7-oxo-1-(trimethylsilyl)hept-1-yn-3-yl 2-Naphthoate (24). Propargylic alcohol **15** (25.0 mg, 0.109 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (0.5 mL) and cooled to 0°C . Triethylamine (46.0 μL , 0.327 mmol, 3.00 equiv) was added followed by DMAP (1.30 mg, 10.9 μmol , 10.0 mol %). Next, 2-naphthoyl chloride (25 mg, 0.131 mmol, 1.20 equiv) was added in one portion. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The solvent was removed under a gentle stream of argon, and then, hexane (2 mL) and sat. aq. NaH_2PO_4 (2 mL) were added. After 5 min of vigorous stirring, the organic phase was separated and the aqueous phase was extracted with hexane (2×2 mL). The combined organic phase was dried (Na_2SO_4), filtrated, and concentrated *in vacuo*. The material thus obtained was purified by flash column chromatography (SiO_2 , gradient elution, 0–10% EtOAc in hexane) to give the desired naphthalate **24** (39.0 mg, 0.102 mmol, 93%) as a white solid. The enantiomeric excess (96%) was determined by HPLC analysis using a chiral column (AD-H, *i*-PrOH/hexane, 2:98, 1.0 mL/min): t_r (major) = 13.63 min, t_r (minor) = 12.54 min. R_f (10% EtOAc in hexane, visualized by UV and KMnO_4 stain) = 0.22; $[\alpha]_D^{25} = +6.2$ (c 0.2, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.64 (s, 1H), 8.08 (dd, $J = 8.6, 1.7$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.89 (dd, $J = 8.4, 2.1$ Hz, 2H), 7.64–7.52 (m, 2H), 5.72 (t, $J = 6.2$ Hz, 1H), 3.68 (s, 3H), 2.44 (t, $J = 7.3$ Hz, 2H), 2.07–1.96 (m, 2H), 1.95–1.87 (m, 2H), 0.18 (s, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 173.7, 165.7, 135.8, 132.6, 131.5, 129.6, 128.5, 128.3, 127.9, 127.3, 126.8, 125.5, 102.3, 91.2, 64.6, 51.8, 34.5, 33.6, 20.7, 0.0 (3C); HRESIMS m/z : 405.1492 $[M + Na]^+$ (calcd for $\text{C}_{22}\text{H}_{26}\text{O}_4\text{SiNa}$, 405.1493).

The exact same procedure was followed for the preparation of racemic naphthalate. Yield: 30.0 mg, 78.5 μmol , 72%. The obtained experimental data matched that given for compound **24**.

Methyl (S)-5-((tert-Butyldimethylsilyloxy)hept-6-ynoate (5). Propargylic alcohol **15** (3.90 g, 17.1 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (45 mL). Imidazole (2.33 g, 34.2 mmol, 2.00 equiv) and *tert*-butyldimethylsilyl chloride (3.86 g, 25.6 mmol, 1.50 equiv) were added in a successive manner at room temperature. The reaction mixture was stirred overnight and then the solvent was removed *in vacuo*. The material was dissolved in methanol (172 mL) and then cooled to 0°C . Next, K_2CO_3 (4.74 g, 34.2 mmol, 2.00 equiv) was added in one portion, and the reaction mixture was allowed to warm to room temperature. The reaction was followed by TLC analysis (product is observed just below the starting material

with 5% EtOAc in hexane as the eluent), and when deemed complete by TLC analysis (~ 1 h), the flask was cooled back down to 0°C . The reaction was quenched by the addition of phosphate buffer (132 mL, pH = 7), and the reaction mixture was stirred for 5 min. NaCl (~ 10 g) was added, and the aqueous phase was extracted with hexane (5×50 mL). The combined organic phase was dried (Na_2SO_4), filtrated, and concentrated *in vacuo*. The crude material thus obtained was purified by flash column chromatography (SiO_2 , 5% EtOAc in hexane) to give the desired product **5** (4.21 g, 15.6 mmol, 91%) as a clear oil. The spectroscopic data was in agreement with previously reported data.³³ R_f (5% EtOAc in hexane, visualized by KMnO_4 -stain) = 0.24; $[\alpha]_D^{20} = -36.2$ (c 0.2, MeOH) [Lit.³⁴ $[\alpha]_D^{20} = -36$ (c 0.2, MeOH)]; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 4.35 (td, $J = 6.0, 2.1$ Hz, 1H), 3.65 (s, 3H), 2.37 (d, $J = 2.1$ Hz, 1H), 2.34 (t, $J = 7.2$ Hz, 2H), 1.85–1.65 (m, 4H), 0.88 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 173.9, 85.3, 72.5, 62.4, 51.6, 37.9, 33.8, 25.9, 20.7, 18.3, -5.0, -4.5; HRESIMS m/z : 293.1543 $[M + Na]^+$ (calcd for $\text{C}_{14}\text{H}_{26}\text{O}_3\text{SiNa}$, 293.1543).

Methyl (S,E)-5-((tert-Butyldimethylsilyloxy)-7-iodohept-6-enoate (16). Vinyl iodide **16** was prepared following the procedure by Sulikowski et al.³⁵ Alkyne **5** (100 mg, 0.370 mmol, 1.00 equiv) was dissolved in benzene (7.5 mL), and then, $n\text{Bu}_3\text{SnH}$ (0.30 mL, 1.11 mmol, 3.00 equiv) and AIBN (10.0 mg, 60.9 μmol , 16.5 mol %) were added. The reaction was heated to 80°C (oil bath) for 2 h. The reaction mixture was then cooled to room temperature, and the solvent was removed *in vacuo*. The crude product thus obtained was purified by flash column chromatography (SiO_2 , 1% Et_2O in hexane) to give the desired product as a clear oil which was used directly in the next reaction. R_f (5% Et_2O in hexane, visualized with KMnO_4 stain) = 0.35.

To a solution of the stannane intermediate (170 mg, 0.303 mmol, 1.00 equiv) in dry CH_2Cl_2 (1.2 mL) was added dropwise a solution of I_2 (115 mg, 0.454 mmol, 1.50 equiv) in dry CH_2Cl_2 (1.7 mL) until the resulting solution maintained a slight pink color. The reaction was stirred for an additional 20 min, followed by the addition of sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (3 mL), H_2O (2 mL), and sat. aq. NaHCO_3 (3 mL). The mixture was stirred for an additional 5 min, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phase was dried (MgSO_4), filtrated, and concentrated *in vacuo*. The crude product thus obtained was purified by flash column chromatography (SiO_2 , 5% Et_2O in hexane) to obtain the vinyl iodide **16** (109 mg, 0.274 mmol, 74% over two steps) as a clear oil. The spectroscopic data was in agreement with previously reported data.³⁵ R_f (5% Et_2O in hexane, visualized by UV and KMnO_4 stain) = 0.23; $[\alpha]_D^{20} = -25.8$ (c 1.7, CHCl_3) [Lit.³⁵ $[\alpha]_D^{20} = -25.8$ (c 1.7, CHCl_3)]; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.50 (dd, $J = 14.4, 6.0$ Hz, 1H), 6.22 (dd, $J = 14.4, 1.3$ Hz, 1H), 4.10 (app qd, $J = 5.9, 1.3$ Hz, 1H), 3.67 (s, 3H), 2.31 (t, $J = 7.3$ Hz, 2H), 1.86–1.56 (m, 2H), 1.56–1.46 (m, 2H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 174.0, 148.9, 76.2, 74.9, 52.2, 36.9, 34.0, 25.9 (3C), 20.4, 18.3, -4.4, -4.8; HRESIMS m/z : 421.0666 $[M + Na]^+$ (calcd for $\text{C}_{14}\text{H}_{27}\text{IO}_3\text{SiNa}$, 421.0666).

Methyl (S,E)-5-((tert-Butyldimethylsilyloxy)-12-(trimethylsilyl)dodeca-6-en-8,11-diyenoate (17). Vinyl iodide **16** (818 mg, 2.05 mmol, 1.00 equiv) was dissolved in THF (11 mL). The solution was cooled to 0°C before Pd(PPh_3) $_2\text{Cl}_2$ (72.1 mg, 0.103 mmol, 5.0 mol %), CuI (46.9 mg, 0.246 mmol, 12.0 mol %), and Et_3N (416 mg, 0.57 mL, 4.11 mmol, 2.00 equiv) were added. The alkyne **4** (702 mg, 0.89 mmol, 5.15 mmol, 2.50 equiv) was dissolved in THF (0.63 mL) and added dropwise. The reaction mixture was allowed to slowly warm to ambient temperature and stirred in the dark for an additional 16 h. After completion, the reaction mixture was filtrated through a short plug of silica gel (15% EtOAc in hexane) and concentrated *in vacuo*. The crude product thus obtained was purified by flash column chromatography (SiO_2 , 5% EtOAc in hexane) to obtain the coupled product **17** (820 mg, 2.02 mmol, 98%) as an orange/brown oil. R_f (5% EtOAc in hexane, visualized by UV and KMnO_4 stain) = 0.25; $[\alpha]_D^{25} = -0.7$ (c 0.7, benzene); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.07 (dd, $J = 15.9, 5.6$ Hz, 1H), 5.65–6.60 (m, 1H), 4.19–4.15 (m, 1H), 3.66 (s, 3H), 3.33 (app d, $J = 2.2$ Hz, 2H), 2.29 (t, $J = 7.4$ Hz, 2H),

1.69–1.61 (m, 2H), 1.54–1.48 (m, 2H), 0.89 (s, 9H), 0.16 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 174.0, 146.0, 109.1, 99.8, 85.4, 83.5, 79.1, 72.3, 51.6, 37.3, 34.1, 26.0 (3C), 20.5, 18.3, 11.7, 0.1 (3C), –4.3, –4.7; HRESIMS m/z : 429.2251 $[\text{M} + \text{Na}]^+$ (calcd for $\text{C}_{22}\text{H}_{38}\text{O}_3\text{Si}_2\text{Na}$, 429.2252).

Methyl (5*E*,8*E*-5-((*tert*-Butyldimethylsilyloxy)dodeca-6-ene-8,11-diyne) (18). The TMS-protected acetylene **17** (66.0 mg, 0.162 mmol, 1.00 equiv) was dissolved in THF (2.55 mL) and EtOH (1.54 mL). A solution of AgNO_3 (190 mg, 0.642 mmol, 3.90 equiv) in a mixture of EtOH and H_2O (1:1, 1.80 mL) was added dropwise and stirred for 40 min. The reaction mixture went from dark yellow to black after the addition of the AgNO_3 solution. KCN (73.8 mg, 1.13 mmol, 7.00 equiv) was dissolved in H_2O (1.3 mL) and added dropwise at room temperature (precipitation was observed during this stage). The reaction was stirred for 2 h and quenched by the addition of H_2O (20 mL) and diluted by EtOAc (30 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 \times 30 mL). The combined organic phase was dried (Na_2SO_4), filtrated, and concentrated *in vacuo*. The crude product thus obtained was purified by flash chromatography (SiO_2 , 5% EtOAc in hexane) to obtain product **18** (35.3 mg, 0.105 mmol, 65%) as a yellow oil. R_f (10% EtOAc in hexane, visualized by UV and KMnO_4 stain) = 0.21; $[\alpha]_{\text{D}}^{25} = -1.8$ (c 0.6, benzene); ^1H NMR (400 MHz, CDCl_3): δ 6.08 (dd, $J = 15.8, 5.4$ Hz, 1H), 5.63 (dq, $J = 15.9, 2.0$ Hz, 1H), 4.17 (qd, $J = 5.7, 1.6$ Hz, 1H), 3.66 (s, 3H), 3.30 (t, $J = 2.4$ Hz, 2H), 2.30 (t, $J = 7.4$ Hz, 2H), 2.08 (t, $J = 2.7$ Hz, 1H), 1.69–1.60 (m, 2H), 1.53–1.47 (m, 2H), 0.90 (s, 9H), –0.04 (s, 3H), –0.02 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 174.1, 146.3, 108.8, 83.1, 79.3, 78.2, 72.2, 69.0, 51.6, 37.2, 34.1, 26.0 (3C), 20.5, 18.3, 10.4, –4.4, –4.8; HRESIMS m/z : 357.1855 $[\text{M} + \text{Na}]^+$ (calcd for $\text{C}_{19}\text{H}_{30}\text{O}_3\text{SiNa}$, 357.1856).

Methyl (5*S*,6*E*,13*E*,15*S*,17*Z*)-5,15-Bis((*tert*-butyldimethylsilyloxy)icoso-6,13,17-trien-8,11-diyne) (19). Vinyl iodide **3** (51 mg, 0.14 mmol, 1.0 equiv) was dissolved in THF (1.0 mL), and the solution was cooled to 0 °C before $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (5.0 mg, 7.1 μmol , 5.0 mol %), CuI (3.0 mg, 15 μmol , 11 mol %), and Et_3N (52 mg, 40 μL , 0.28 mmol, 2.0 equiv) were added. Alkyne **18** (56 mg, 0.17 mmol, 1.2 equiv) was dissolved in THF (1.0 mL) and added dropwise. The reaction mixture was allowed to slowly warm up to rt and stirred in the dark for 16 h. After completion, the reaction mixture was filtrated through a plug of silica gel (15% EtOAc in hexane) and concentrated *in vacuo*. The crude product thus obtained was purified by flash chromatography (SiO_2 , gradient elution, 2.5–5% EtOAc in hexane) to obtain product **19** (62 mg, 0.11 mmol, 78%) as a clear oil. R_f (10% EtOAc in hexane, visualized by UV and KMnO_4 stain) = 0.40; $[\alpha]_{\text{D}}^{20} = +1.9$ (c 0.30, benzene); ^1H NMR (400 MHz, CDCl_3): δ 6.12 (dd, $J = 15.9, 5.2$ Hz, 1H), 6.07 (dd, $J = 15.9, 5.5$ Hz, 1H), 5.69–5.61 (m, 2H), 5.50–5.42 (m, 1H), 5.35–5.27 (m, 1H), 4.19–4.13 (m, 2H), 3.66 (s, 3H), 3.42 (t, $J = 2.2$ Hz, 2H), 2.30 (t, $J = 7.4$ Hz, 2H), 2.27–2.18 (m, 2H), 2.02 (pd, $J = 7.2, 1.5$ Hz, 2H), 1.69–1.61 (m, 2H), 1.52–1.47 (m, 2H), 0.95 (t, $J = 7.5$ Hz, 3H), 0.89 (s, 18H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 174.1, 146.2, 146.1, 134.1, 124.2, 109.0, 108.6, 83.8, 83.6, 79.2, 79.0, 72.6, 72.2, 51.6, 37.2, 36.0, 34.1, 26.0 (6C), 20.9, 20.5, 18.4, 18.3, 14.3, 11.3, –4.4, –4.5, –4.7, –4.8; HRESIMS m/z : 595.3608 $[\text{M} + \text{Na}]^+$ (calcd for $\text{C}_{33}\text{H}_{56}\text{O}_4\text{Si}_2\text{Na}$, 595.3609).

Methyl (5*S*,6*E*,8*Z*,11*Z*,13*E*,15*S*,17*Z*)-5,15-Bis((*tert*-butyldimethylsilyloxy)icoso-6,8,11,13,17-pentaenoate) (20). Diyne **19** (10 mg, 18 μmol , 1.0 equiv) was dissolved in a mixture of EtOAc/pyridine/1-octene (10:1:1, 0.3 mL) under argon. Lindlar's catalyst (7.0 mg) was added, and the flask was evacuated and refilled with hydrogen gas twice. After 1 h, additional Lindlar's catalyst (7.0 mg) was added. The reaction was stirred for another 4 h and filtrated through a short plug of silica gel (15% EtOAc in hexane) and concentrated *in vacuo*. The crude product thus obtained was purified by flash chromatography (SiO_2 , 1% EtOAc in hexane) to obtain product **20** (7.0 mg, 12 μmol , 70%) as a pale yellow oil. R_f (10% EtOAc in hexane, visualized by UV and KMnO_4 stain) = 0.38; $[\alpha]_{\text{D}}^{20} = +36.8$ (c 0.25, benzene); ^1H NMR (400 MHz, CDCl_3): δ 6.49–6.40 (m, 2H), 5.99 (app td, $J = 10.9, 2.0$ Hz, 2H), 5.68 (dd, $J = 15.2, 5.9$ Hz, 1H), 5.64 (dd, $J = 15.2, 6.2$ Hz, 1H), 5.49–5.32 (m, 4H), 4.21–

4.16 (m, 2H), 3.66 (s, 3H), 3.05 (app t, $J = 7.4$ Hz, 2H), 2.32 (t, $J = 7.3$ Hz), 2.28–2.22 (m, 2H), 2.03 (app p, $J = 7.4$ Hz, 2H), 1.72–1.64 (m, 2H), 1.53–1.49 (m, 2H), 0.95 (t, $J = 7.5$ Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.06 (2 \times s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 174.2, 137.3, 137.2, 133.7, 129.3, 129.1, 128.7, 128.6, 124.8, 124.6, 124.3, 73.2, 72.9, 51.6, 37.8, 36.5, 34.2, 26.6, 26.4 (6C), 20.9 (2C), 18.4 (2C), 14.4, –4.1, –4.3, –4.6, –4.6; HRESIMS m/z : 599.3922 $[\text{M} + \text{Na}]^+$ (calcd for $\text{C}_{33}\text{H}_{60}\text{O}_4\text{Si}_2\text{Na}$, 599.3922).

Methyl (5*S*,6*E*,8*Z*,11*Z*,13*E*,15*S*,17*Z*)-5,15-Dihydroxyicoso-6,8,11,13,17-pentaenoate (2). The bis-TBS-protected intermediate **20** (10 mg, 17 μmol , 1.0 equiv) was azeotroped with 2-MeTHF (2 \times 1 mL) and then cooled to 0 °C before a solution of AcCl in dry MeOH (0.13 mL, 2.6 mmol, 15 mol %) was added (the solution was prepared just prior to use by adding freshly distilled AcCl (3.0 μL) to dry MeOH (2.0 mL) under argon). The reaction mixture was stirred for 4 h at 0 °C. The reaction mixture was diluted with CH_2Cl_2 (0.3 mL) prior to neutralization with a 10% aq. solution of NaHCO_3 (20 μL) and washed with H_2O (0.2 mL). The organic phase was dried (Na_2SO_4), filtrated, and concentrated *in vacuo*. The crude product thus obtained was purified by flash chromatography (SiO_2 , 40% EtOAc in hexane) to afford the RvE4 methyl ester (**2**, 4.0 mg, 12 μmol , 66%) as a clear oil. The chemical purity (>97%) was determined by HPLC analysis (Eclipse XDB-C18, MeOH/ H_2O 76:24, 1.0 mL/min): t_r (minor) = 7.88, 10.89 and 11.69 min, and t_r (major) = 9.37 min. R_f (40% EtOAc in hexane, visualized by UV and KMnO_4 stain) = 0.17; $[\alpha]_{\text{D}}^{20} = +8.4$ (c 0.5, MeOH); UV–Vis (MeOH) λ_{max} 242 nm (log $\epsilon = 4.64$); ^1H NMR (400 MHz, MeOD): δ 6.61–6.54 (m, 2H), 6.01 (td, $J = 11.0, 4.9$ Hz, 2H), 5.69 (app ddd, $J = 15.5, 9.2, 6.5$ Hz, 2H), 5.51–5.34 (m, 4H), 4.13 (p, $J = 6.8$ Hz, 2H), 3.66 (s, 3H), 3.10 (tt, $J = 7.5, 1.7$ Hz, 2H), 2.36 (t, $J = 7.2$ Hz, 2H), 2.35–2.27 (m, 2H), 2.06 (app dp, $J = 7.4, 0.8$ Hz, 2H), 1.73–1.63 (m, 2H), 1.57–1.51 (m, 2H), 0.96 (t, $J = 7.5$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, MeOD): δ 175.8, 137.8, 137.5, 134.6, 130.3, 130.2, 129.6 (2C), 126.3 (2C), 125.5, 73.2, 72.8, 52.0, 37.6, 36.3, 34.6, 27.4, 22.1, 21.7, 14.5; HRESIMS m/z : 371.2192 $[\text{M} + \text{Na}]^+$ (calcd for $\text{C}_{21}\text{H}_{32}\text{O}_4\text{Na}$, 371.2193).

LC–MS/MS MRM Matching Experiments. Following a literature procedure,³⁶ a solution of RvE4 methyl ester (**2**, 5.0 μg , 14 nmol) in MeOH was concentrated under a gentle stream of nitrogen gas, dissolved in THF (500 μL), and cooled to –78 °C. To the resulting solution was added 1 M LiOH (50 μL , 50 μmol) and distilled water (one drop, ~ 20 μL) and the reaction mixture was stirred in a 4 °C cold room for 24 h. The reaction mixture was then concentrated under a gentle stream of nitrogen gas and reconstituted with MeOH (500 μL). The identity of the compound was verified by UV–Vis and LC–MS/MS. The chemical yield of the RvE4 free acid **1** was 69% (3.3 μg , 9.9 nmol) post saponification (based on UV–Vis) and was determined to be >95% pure by targeted MRM LC–MS/MS. The physical properties of synthetic RvE4 (**1**) and biogenic RvE4 (**1**) were analyzed on a QTRAP 5500 mass spectrometer (Sciex, Framingham, MA, USA) equipped with a LC20AD UFLC (Shimadzu, Tokyo, Japan) with a Poroshell EC-C18 column (100 mm \times 4.6 mm \times 2.7 μm ; Agilent Technologies, Santa Clara, CA, USA) kept at 50 °C. RvE4 (**1**) was monitored by targeted multiple reaction monitoring (m/z 333 > 115) and enhanced product ion mode in negative polarity. RvE4 (**1**) was eluted at a flow rate of 0.5 mL/min with a gradient of LC–MS grade methanol/water/acetic acid from 50/50/0.01 v/v/v to 98/2/0.01 v/v/v. Data were acquired and analyzed with Analyst version 1.6.2 (Sciex).⁸

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.0c02913>.

^1H -, ^{13}C NMR, and UV–Vis data of RvE4 methyl ester (**2**) and all synthetic intermediates (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The scholarship to A.F.R. by the Department of Pharmacy is gratefully acknowledged. M.A. gratefully acknowledges the Research Council of Norway (RCN) for a grant (FRINATEK, 262901). This work was partly supported by the Research Council of Norway through the Norwegian NMR Package in 1994 and partly supported by the Research Council of Norway through the Norwegian NMR Platform, NNP (226244/F50). C.N.S. contributions are supported by NIH grant R01GM038765 (USA) and NIH Program Project P01GM095467 (USA).

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