Total Synthesis of 34-Hydroxyasimicin and Its Photoactive Derivative for Affinity Labeling of the Mitochondrial Complex I

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Abstract: The asymmetric total synthesis of the 34-hydroxyasimicin and its 3-(4-benzoylphenyl)propionate ester was achieved by means of a convergent synthetic strategy. This ester, which contains eight asymmetric centers, represents the first photoaffinity-labeling agent that is derived from an Annonaceous acetogenin. The key transformations in the synthesis include the Sharpless asymmetric dihydroxylation reaction, the Wittig olefination reaction, an oxidative cyclization reaction with rhenium(VII) oxide, the Williamson etherification reaction, and a palladium-catalyzed cross-coupling reaction. Use of the target molecule for photoaffinity-labeling studies of bovine mitochondrial NADH-ubiquinone oxidoreductase (Complex I) may shed light on the structure/function of this intricate enzyme and on the origin of the high antitumor activity exhibited by the Annonaceous acetogenins.

Keywords: acetogenins · dihydroxylation · mitochondria · photoaffinity labeling · rhenium

Introduction

NADH-ubiquinone oxidoreductase, also known as Complex I, is one of four multisubunit enzyme complexes of the respiratory chain in the mammalian mitochondria that form the electron-transport chain from NADH to oxygen and generate the energy source ATP.[1] Complex I, which bears one noncovalently bound flavin mononucleotide (FMN) and eight iron–sulfur clusters with a total molecular mass of approximately 1 000 000 Da, is one of the most intricate enzyme complexes known, consisting of more than 46 protein subunits, seven of which are encoded in the mitochondrial genome, while the others originate from the nuclear DNA.[2,3] The complex spans the inner-mitochondrial membrane, generating a proton gradient across the membrane by translocation of protons from the matrix side of the membrane to the cytoplasm. Since structural and functional defects of Complex I are reported to be a primary cause in many diseases, including a wide variety of degenerative diseases, aging, and cancer, the structure and catalytic mechanism of this enzyme complex have attracted an ever growing attention.[4]. The three-dimensional images of Complex I from *N. Crassa* and *E. Coli* were achieved by electron microscopy.[5]

Due to the lack of detailed structural information about Complex I (and about its bacterial analogue, NDH-1), very little is known about the electron pathways from matrix NADH to membrane ubiquinone. The clues linking this process with the translocation of protons are highly controversial.[6] Different types of inhibitors (Scheme 1) have been used in an effort to dissect the electron and proton pathways of this complicated enzyme system.[7] For example, the use of two rotenone-derived photoaffinity probes have located a single inhibitor-binding site in the ND1 subunit.[8] Likewise, photoaffinity labeling with a fenpyroximate[9] derivative specifically labeled the ND5 subunit of Complex I.[10] Other subunits were specifically labeled with a ^{14}C-tagged *N,N′*-dicyclohexylcarbodiimide,[11] a ubiquinone derivative,[12] and pyridaben derivative.[13,14] Consequently, the subunits IP49 K, PSST, ND1, ND3, and ND5 were proposed to comprise an inhibitor-binding pocket in either Complex I or in NDH-1.[15]

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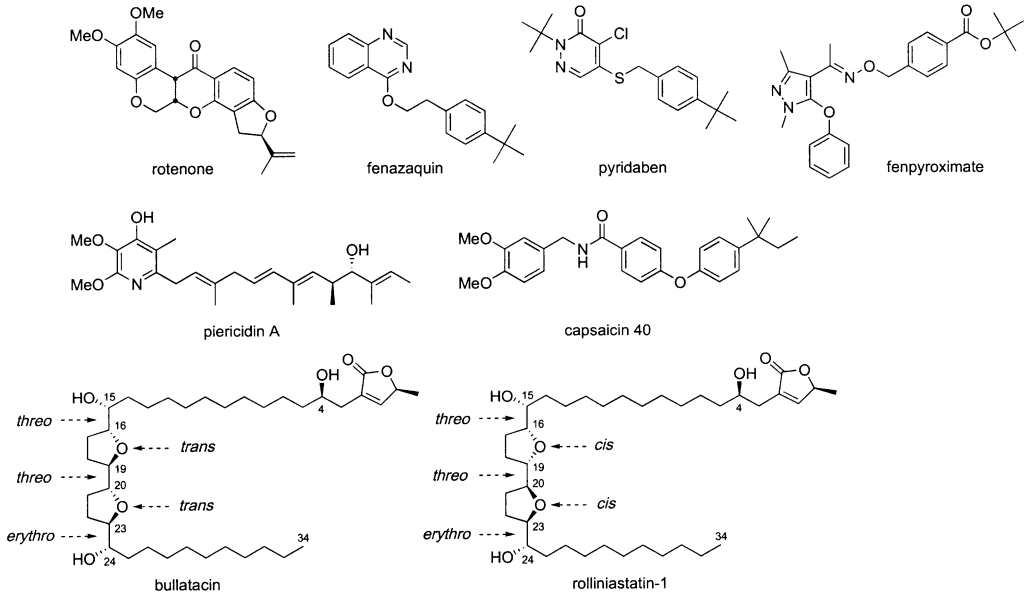


Scheme 1. Reported inhibitors of Complex I.

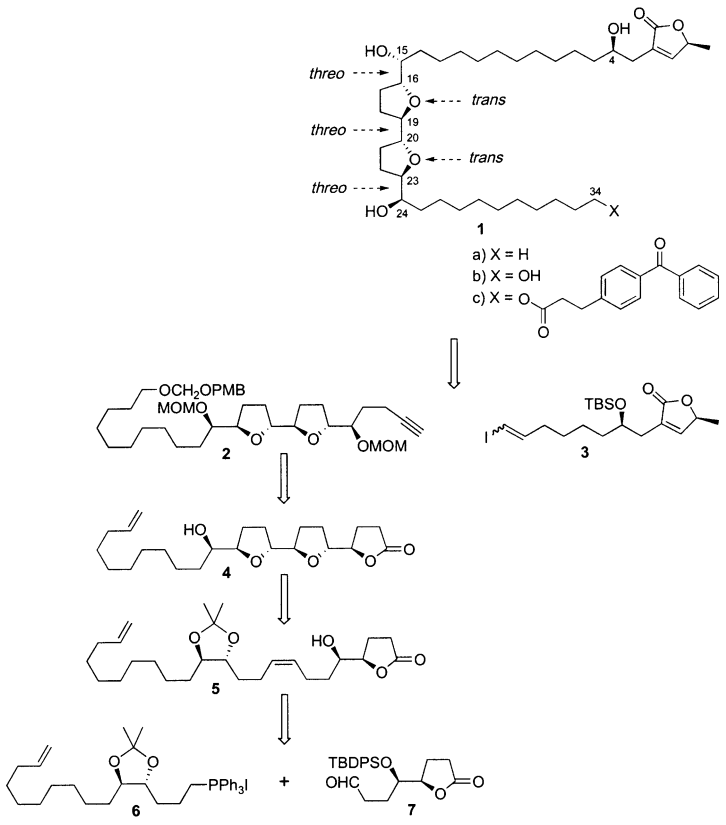
Of particular interest are the Annonaceous acetogenins, which were found to be the most powerful inhibitors of the mammalian Complex I and of the insect mitochondrial electron-transport systems.[16] These natural products are known not only for their antitumor activity, but also for being potent antimalarial, immunosuppressive, pesticidal, and antifeedant agents.[17] More than 350 acetogenins have already been isolated from 37 species in the Annonaceae, a family of tropical trees and shrubs that accommodates over 2300 species.[18] While most of these fatty acid derivatives exhibit remarkable structural diversity, they share very similar carbon skeletons, with the main variations being the relative and absolute configuration of the various stereogenic oxygen functions. For example, a dominant structural feature that appears in more than 40% of the Annonaceous acetogenins is a ten-carbon fragment that contains two adjacent tetrahydrofuran rings flanked by either one or two hydroxyl groups. A long alkyl chain tethers this fragment to a butenolide group, which represents the conserved part of almost all acetogenins.

The strong inhibitory potency of these compounds and their structural diversity make them interesting tools to investigate the structure–function problems of Complex I. Furthermore, previous reports have suggested that the various acetogenins inhibit Complex I in different ways,[16c,19] a rather surprising observation on grounds of the very close chemical resemblance among them. For example, the closely related rolliniastatin-1, rolliniastatin-2 (bullatacin), and corossolin were found to inhibit Complex I with different kinetic features reflecting differential binding modes.[20] These observations offer interesting opportunities in both mechanistic investigations and drug discovery, particularly since few of these compounds have shown in vitro antitumor potency 10^8 times greater than that of adriamycin.[21] Nevertheless, attempts to photolabel Complex I with an acetogenin derivative have not yet been reported, probably because the synthesis of such derivatives is much more difficult than that of the other inhibitors.

Here we report on the first synthesis of a photoaffinity-labeling agent for Complex I that is derived from the Annonaceous acetogenins. Our design is based on the skeleton of asimicin (**1a**, Scheme 2), the synthesis of which was reported earlier.[22] Asimicin was first isolated from extracts of the bark and seeds of the pawpaw tree, *Asimina triloba* Dunal, by using brine shrimp lethality for activity-directed fractionation.[23] It was found to be extremely cytotoxic in the 9KB (human nasophyraneal carcinoma, $ED_{50} < 10^{-5}$ μg mL^{-1}) and the 9BS (murine lymphocyte leukemia, $ED_{50} < 10^{-7}$ μg mL^{-1}) system. Bullatacin, which is an epimer of asimicin at position 24, has also shown antitumor potential in vitro against HL-60 cells that are resistant to adriamycin,[24] and in vivo with mice bearing L1210 murine leukemia and with mice bearing A2780 conventional ovarian cancer xenografts.[25] Both asimicin and bullatacin were found to be potent inhibitors of Complex I.[16]

Abstract in Hebrew:

החומר 34-הידרוכסיאסימיצין וכן האסטר, אשר נגזר ממנו ומחומצה 3-(4-בנזואילפניל) פרופיונית, הוכנו בסינתזה אסימטרית טוטלית, תוך שימוש באיסטרטגיה מתכנסת. האסטר הנ״ל, אשר מכיל 6 מרכזים אסימטריים, מייצג את הסמן הפוטואפיני הראשון, אשר הוכן על בסיס של אצטוגנין אנוני. שלבי המפתח במהלך הסינתזה כוללים את הדיהידרוכסילציה האסימטרית של שרפלס, תגובת האולפינציה של וויטיג, תגובת הציקליזציה המחמצנת באמצעות תחמוצת רניום(VII), תגובת האתריפיקציה של וויליאמסון, ותגובת צילוב, אשר מזורזת ע״י קומפלקס פלאדיום. השימוש בנגזרת פוטואפינית של אסימיצין, כדי לסמן באופן ייחודי את המערכת האנזימתית המיטוכונדרית, הידועה בשם יוביקווינון NADH-יוביקווינון רדוקטאז הידועה בשם (קומפלקס I) עשוי לשפוך אור על המבנה והפעילות של מערכת מורכבת זאת. יתר על כן, הסימון הפוטוכימי עשוי להצביע על מקור הפעילות הגבוהה של האצטוגנינים האנוניים כחומרים אנטי-סרטניים.



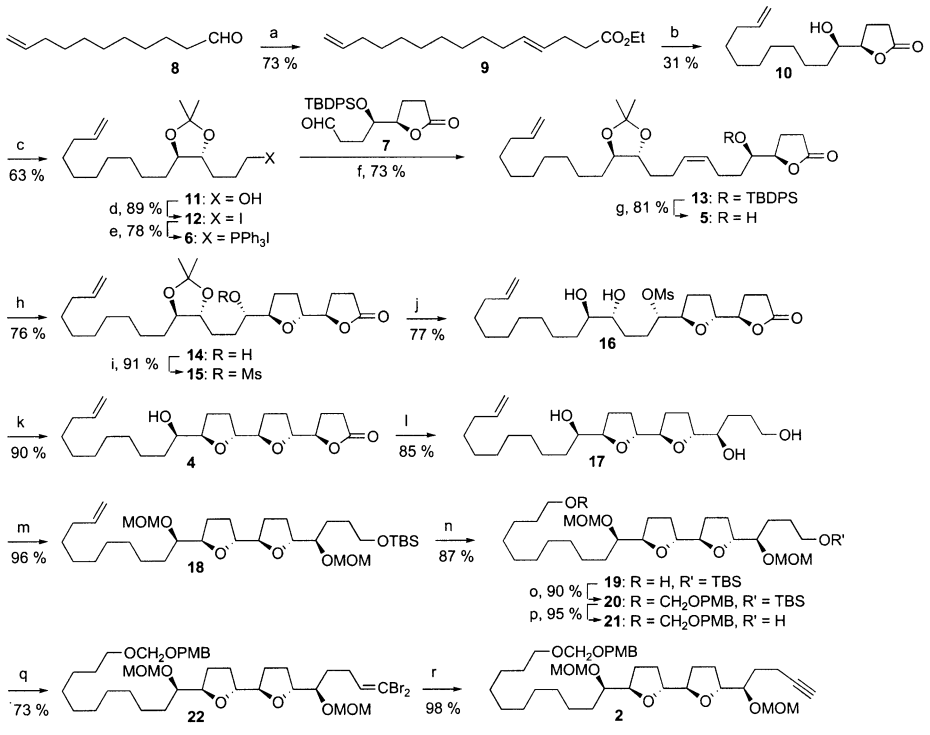
Scheme 2. Retrosynthetic analysis of 34-hydroxyasimicin.

The decision concerning the attachment point of the photoactive device was nontrivial, because the detailed mode of action and the binding orientation of the Annonaceous acetogenins are yet unknown. Since the butenolide fragment is highly conserved in most of the acetogenins, one could assume that in order to retain the inhibitory activity the butenolide fragment should remain intact. Furthermore, studies on acetogenin analogues in which the butenolide fragment was replaced by a ubiquinone ring have indicated that the butenolide moiety of natural acetogenins binds to the ubiquinone reduction site of the enzyme.[26] Similar arguments also hold true for the bis-THF fragment of the molecule, because small variations in the stereogenic centers of this fragment are known to cause significant changes in the biological activity. Furthermore, the length of the polymethylene chain that links both functional fragments was also found to be essential for activity. Consequently, the only part of the molecule that could suffer the required modification with minimal loss of activity seemed to be the end of the alkyl chain. Accordingly, our target molecule (**1c**) was designed to contain a benzophenone group attached by a flexible linkage to position 34 of the molecule. We decided to use the benzophenone label, because it offers the advantage of being more reactive than other photolabeling devices, such as diazo and azide groups, with preferential reactivity towards C–H over X–H bonds.[27] In addition, diazo and azide compounds are activated irreversibly at 245 nm, while benzophenone is activated reversibly at 350–365 nm, and is also more chemically and room light stable. Furthermore, labeling efficiencies for nitrenes and carbenes are typically in the range of 5–10%, whereas they are much higher for benzophenyl radical.

Results and Discussion

In our previous studies on the total synthesis of adjacent bis-THF acetogenins as well as other natural and non-natural acetogenins, including solamin, reticulatacin, asimicin, bullatacin, trilobin, trilobacin, squamotacin, rolliniastatin, uvaricin, rollidecins C and D, mucocin, goniocin, 17,18-bis-epigoniocin, and cyclogoniodenin T,[22,28] we met the synthetic challenges by examining three general synthetic strategies: the "naked" carbon-skeleton strategy,[29] the convergent approach, and a hybrid strategy that combines the advantages of the first two.[30] In principle, all three approaches can be generally used for the synthesis of **1b** and **1c** as well as their diastereomers. In this work we have chosen the convergent strategy, which is outlined in the retrosynthetic analysis (Scheme 2). The analysis dissects the target molecule into two major fragments, the bis-THF fragment (**2**) and the butenolide moiety (**3**). Assembly of these building blocks could be achieved by a palladium-catalyzed cross-coupling reaction.[31] The butenolide intermediate (**3**) was obtained by previously described methods,[22] and alkyne **2** was prepared from the corresponding tricyclic intermediate **4**. The synthesis of **4** represents the most significant component of the entire synthesis, not only because it contains as many as six asymmetric centers, but also because the potential stereomeric variability of this fragment represents the origin of diversity in the bis-THF subgroup of the Annonaceous acetogenins. We envisioned the preparation of **4** from alkene **5**, which, in turn, could be obtained by Wittig coupling from phosphonium salt **6** and aldehyde **7**. This last compound was prepared previously in seven steps from 1,4-dihydroxybutane.[22]

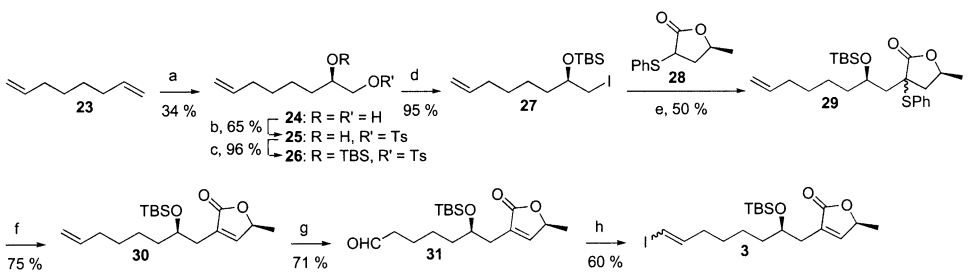
The synthesis of intermediate **2** (Scheme 3) started with undec-10-enal (**8**), which was treated with vinyl magnenium bromide. Treatment of the resultant allylic alcohol with triethyl orthoacetate in the presence of a catalytic amount of propionic acid produced the γ,δ-unsaturated ester **9** by means of the Claisen-Johnson rearrangement. The Sharpless asymmetric dihydroxylation (AD) reaction of **9** with AD-mix-β, followed by base and acid treatment afforded hydroxylactone **10** with >95% *ee*, which was increased to essentially 100% *ee* in one crystallization step. Lithium aluminum hydride (LAH) reduction afforded the corresponding triol,



Scheme 3. Synthesis of intermediate **2**. Key: a) i) Vinylmagnesium bromide, THF, 0°C, 0.5 h; ii) $(EtO)_3CCH_3$, propionic acid, xylene, reflux, 2 h; b) i) AD-mix-β, $MeSO_2NH_2$, *t*BuOH/water (1:1), 0°C, 12 h; ii) Aqueous KOH (3N), MeOH, 60°C, 2 h, then HCl (3N); iii) TsOH (5%), CH_2Cl_2, RT, 1 h; c) i) $LiAlH_4$, diethyl ether/THF, 0°C, then reflux, 2 h; ii) acetone/hexane (1:2), TsOH (cat); d) I_2, imidazole, PPh_3, CH_2Cl_2, RT, 2 h; e) I_2, PPh_3, $NaHCO_3$, CH_3CN, reflux, 16 h; f) NaHMDS, THF, HMPA, −78°C, 2 h, then **7**, −78°C to RT, 16 h; g) TBAF, THF, 0°C to RT, 2 h; h) Re_2O_7, lutidine, CH_2Cl_2, 12 h; i) MsCl, Et_3N, CH_2Cl_2, −30°C, 0.5 h; j) TsOH, MeOH-H_2O (4:1), RT, 16 h; k) pyridine, reflux, 3 h; l) $LiAlH_4$, diethyl ether/THF, 0°C, then reflux, 2 h; m) TBSCl, *i*Pr_2NEt, DMAP, CH_2Cl_2, 0°C to RT, 12 h, then $ClCH_2OMe$, *i*Pr_2NEt, 0°C to RT, 16 h; n) 9-BBN, THF, 0°C to RT, 4 h, then H_2O_2 (35%), aq NaOH (3N), 0°C, 1 h; o) *p*-$MeOC_6H_4CH_2OCH_2Cl$, *i*Pr_2NEt, CH_2Cl_2, 0°C to RT, 3 h; p) TBAF, THF, 0°C to RT, 2 h; q) i) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, 1 h, then Et_3N, −78°C to 0°C; ii) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, 0°C, 16 h; r) EtMgBr, THF, 0°C, 0.5 h.

in which the vicinal diol was protected in the form of an acetonide derivative, **11**. The unprotected primary alcohol in **11** was converted to the corresponding iodide, **12**, which was then treated with triphenylphosphine to produce the phosphonium salt **6**. Wittig reaction between **6** and aldehyde **7**[22] was carried out in the presence of sodium hexamethyldisilazide to afford the *cis*-alkene **13**. Cleavage of the *tert*-butyldiphenylsilyl group in **13** with tetrabutyl ammonium fluoride (TBAF) produced alcohol **5**, one of the key intermediates of this synthetic scheme. Oxidative cyclization with CF_3CO_3-ReO_3 and lutidine provided the *trans*-THF ring in **14**[32] as a single diastereomer in 76% yield. Activation of the free hydroxyl group in **14** in the form of a mesylate (**15**), followed by acid-catalyzed hydrolysis of the acetonide group produced the free diol (**16**). Heating compound **16** in pyridine affected the Williamson-type etherification to produce the tricyclic intermediate **4**. LAH reduction afforded triol **17**, in which the primary alcohol was protected in the form of a *tert*-butyldimethylsilyl ether, while the two secondary alcohols were converted to methoxymethyl ethers to afford **18**. Hydroboration of the terminal double bond of **18** afforded alcohol **19**, which was protected in the form of 4-methoxybenzyloxymethyl ether to give **20**. The *tert*-butyldimethylsilyl ether was then cleaved to afford alcohol **21**, which was oxidized to give the corresponding aldehyde. The aldehyde was immediately treated with PPh_3-CBr_4 in the presence of triethylamine to produce the 1,1-dibromoalkene **22**. Finally, treatment of **22** with EtMgBr provided the desired key intermediate **2**.[33]

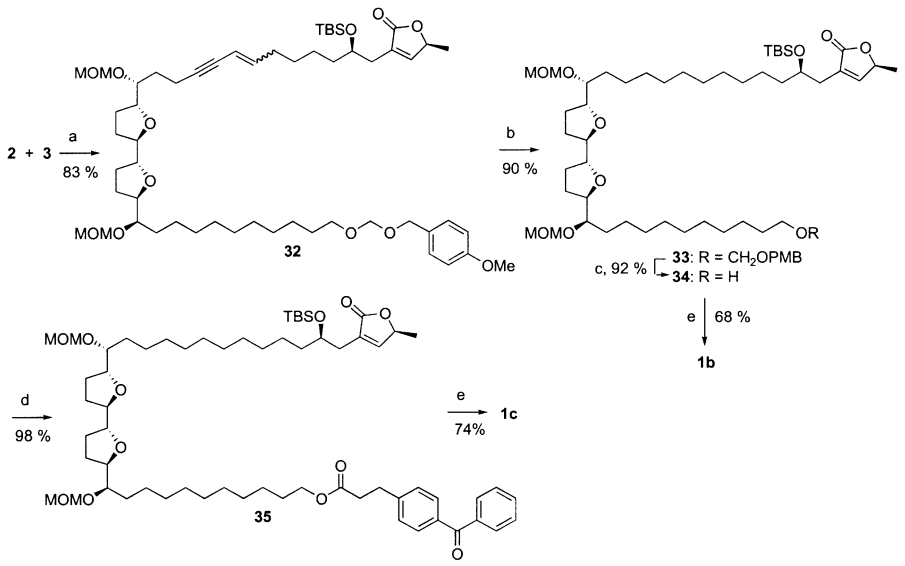
The synthesis of the butenolide fragment **3** (Scheme 4) started from octa-1,7-diene (**23**) by using our previously described methods for the preparation of homologous compounds.[22] Thus, dihydroxylation with AD-mix-β using pyrimidine ligand afforded diol **24**. The primary hydroxyl was selectively converted to the corresponding tosylate **25**, and the secondary hydroxyl was protected in the form of a silyl ether (**26**) by using TBSOTf at low temperature. The tosylate group was then converted to iodide **27** by using NaI in refluxing acetone. Lactone **28**[34] was alkylated with iodide



Scheme 4. Synthesis of the butenolide fragment, **3**. a) i) AD-mix-β, *t*BuOH/water (2:1), 0°C, 18 h; b) TsCl, collidine, 0°C, 16 h; c) TBSOTf, lutidine, CH_2Cl_2, −78°C, 3 h; d) NaI, $NaHCO_3$ acetone, reflux, 36 h; e) LDA, THF, HMPA, compound **28**, −78°C, then compound **27**, RT, 24 h; f) i) *m*-CPBA, CH_2Cl_2, 0°C, 10 min; ii) toluene, 90°C, 2 h; g) OsO_4, THF/H_2O, then $NaIO_4$, 2.5 h; h) CHI_3, $CrCl_2$, THF, 0°C, 4 h.

27 with LDA in THF-HMPA to produce sulfide **29**, which in turn was oxidized with *m*-CPBA; the resultant sulfoxide was heated in toluene at 90 °C to produce the butenolide **30**. Selective dihydroxylation of the monosubstituted double bond in **30** with OsO_4 followed by oxidative cleavage with $NaIO_4$ produced aldehyde **31**. Finally, olefination with iodoform and chromium dichloride afforded the desired vinyl iodide **3** in the form of a mixture of the *E*/*Z* isomers.[35]

The target molecules **1b** and **1c** were assembled from intermediates **2** and **3** (Scheme 5) by a Pd^{II}-catalyzed cross-coupling reaction in the presence of CuI and Et_3N to produce the eneyne intermediate **32**.[31] Hydrogenation over Wilkinson's catalyst afforded the protected acetogenin **33**. Oxidative cleavage of the 4-methoxybenzyloxymethyl ether with DDQ afforded alcohol **34**.[36] Treatment of **34** with $BF_3{\cdot}Et_2O$ in dimethyl sulfide afforded the fully deprotected acetogenin **1b**. Alternatively, alcohol **34** was acylated with 3-(4-benzoylphenyl)propionate[37] in the presence of EDCI and DMAP to produce the corresponding ester **35**, which was then deprotected using $BF_3{\cdot}Et_2O$ in methyl sulfide to afford the photoaffinity label **1c**.



Scheme 5. Synthesis of 34-hydroxyasimicin, **1b** and its photolabeling derivative, **1c**. a) $[Pd(Ph_3P)_2Cl_2]$, CuI, Et_3N, RT, 2 h; b) $[Rh(Ph_3P)_3Cl]$, H_2, benzene/MeOH (6:1), RT, 16 h; c) DDQ, CH_2Cl_2/H_2O, RT, 1 h; d) 3-(4-benzoylphenyl)propionate, EDCI, DMAP, CH_2Cl_2, RT, 16 h; e) $BF_3{\cdot}OEt_2$, Me_2S, 0 °C, 1 h.

In conclusion, the synthesis of the target molecule **1c** was achieved through a convergent strategy in a total of 35 steps, starting with octa-1,7-diene, 1,4-dihydroxybutane, undec-10-enal, and (*S*)-(−)-propylene oxide. While the commercially available (*S*)-(−)-propylene oxide provided the asymmetric center of the butenolide ring, all other stereogenic centers in the target molecule were achieved either by the Sharpless AD reaction (C15, C16, C23, and C24) or by the oxidative cyclization reaction with rhenium(VII) oxide (C19, and C20). Photolabeling studies of bovine mitochondrial Complex I with **1c** are currently underway and the results will be reported shortly.

Experimental Section

General methods: ^1H and ^{13}C NMR spectra were measured in $CDCl_3$. Optical rotations were measured in a one-decimeter (1.3 mL) cell by using an Autopol III automatic polarimeter. TLC was performed on glass sheets precoated with silica gel (Merck, Kieselgel 60, F254, Art. 5715). Column chromatographic separations were performed on silica gel (Merck, Kieselgel 60, 230–400 mesh, Art. 9385) under pressure. All commercially available reagents were used without further purification. Solvents were either used as purchased or distilled using common practices where appropriate. All reactions were carried out under dry Argon.

(*trans*)-Ethyl pentadec-4,14-dienoate (9): Vinylmagnesium bromide (1 M, 96 mL, 96 mmol) was added to a solution of undecylenic aldehyde (13.46 g, 80 mmol) in THF (140 mL) at 0 °C. The mixture was stirred for 0.5 h and then worked up with diethyl ether and saturated aqueous NH_4Cl. Removal of solvents followed by filtration over silica gel (hexanes/ethyl acetate, 4:1) afforded tridec-1, 12-dien-3-ol (16.1 g), which was taken to next step without further purification.

The above-mentioned allylic alcohol (16.1 g), triethyl orthoacetate (24.3 mL, 160 mmol), and propionic acid (0.08 g, 0.017 mmol) were dissolved in xylene (25 mL), and the mixture was refluxed for 2 h. Solvents were removed under reduced pressure, and the residue was distilled to give **9** (15.49 g, 73 %) in the form of a light yellow oil. ^1H NMR (500 MHz): $\delta = 5.85–5.79$ (m, 1H), 5.48–5.38 (m, 2H), 5.01–4.92 (m, 2H), 4.13 (q, $J = 7.3$ Hz, 2H), 2.43–2.30 (m, 2H), 2.28 (t, $J = 4.4$ Hz, 2H), 2.07–2.02 (m, 2H), 1.99–1.95 (m, 2H), 1.39–1.16 ppm (m and br s, 15H); ^{13}C NMR (75 MHz): $\delta = 173.1$, 139.1, 131.7, 127.8, 114.0, 60.2, 34.5, 33.9, 32.6, 29.5, 29.2 (×2), 29.0, 28.0, 14.3 ppm; ESIMS: *m*/*z* calcd for $C_{17}H_{30}O_2$: 266; found: 265 $[M-H]^-$.

(4*R*,5*R*)-5-Hydroxypentadec-14-en-1,4-olide (10): Compound **9** (15.19 g, 57.11 mmol) was added to a cold (0 °C) solution of AD-mix-β (85.61 g) and $MeSO_2NH_2$ (5.49 g, 57.11 mmol) in *tert*-BuOH/water (1:1, 560 mL), and the mixture was stirred at 0 °C for 12 h and then quenched by the addition of sodium metabisulfite (85.67 g). The mixture was worked-up with ethyl acetate and water, solvents were removed under reduced pressure, and the residue was dissolved in methanol (84 mL). Aqueous KOH (3 N, 56 mL) was added, and the mixture was stirred at 60 °C for 2 h, then cooled to 0 °C, acidified with 3 N HCl, and extracted with ethyl acetate. Solvents were removed under reduced pressure, and the residue was dissolved in CH_2Cl_2. *p*-Toluenesulfonic acid (TsOH, 1.57 g) was added, and the mixture was stirred at room temperature for 1 h, worked up with saturated aqueous $NaHCO_3$ and CH_2Cl_2, and purified by column chromatography (silica gel, hexanes/ethyl acetate, 1:1) to give lactone **10** (4.52 g, 31 %) in the form of a white solid. $[\alpha]_D = -23.0$ ($c = 0.98$ in $CHCl_3$); ^1H NMR (300 MHz): $\delta = 5.82–5.71$ (m, 1H), 5.00–4.87 (m, 2H), 4.40 (td, $J = 6.9$, 4.5 Hz, 1H), 3.57–3.51 (m, 1H), 2.66–2.44 (m, 4H), 2.24–2.09 (m, 2H), 2.05–1.98 (m, 2H), 1.55–1.21 ppm (m and br s, 12H); ^{13}C NMR (75 MHz): $\delta = 177.4$, 138.9, 113.9, 83.0, 73.3, 33.7, 32.9, 29.4, 29.4 (×2), 29.0, 28.8, 28.7, 25.5, 23.0 ppm; ESIMS: *m*/*z* calcd for $C_{15}H_{26}O_3$: 254.19; found: 255 $[M+H^+]$, 277 $[M+Na]^-$), 289 $[M+Cl]^-$.

(4*R*,5*R*)-4,5-Isopropylidenedioxy-14-en-pentadecanol (11): $LiAlH_4$ (2.13 g, 53.28 mmol) was added in portion to a solution of **10** (4.52 g, 17.8 mmol) in dry diethyl ether (35 mL) at 0 °C. The mixture was stirred at 0 °C, then refluxed for another 2 h, cooled, diluted with diethyl ether,

and worked up by dropwise addition of water. After all inorganic material was precipitated, the solid was filtered to give crude corresponding triol (3.7 g).

The above-mentioned triol (3.7 g) and TsOH (0.38 g 2.02 mmol) were dissolved in a mixture of acetone/hexane (116 mL, acetone/hexane = 1:2) and the solution was refluxed for 6 h with Dean-Stark apparatus. The reaction mixture was worked up by addition of diethyl ether, removal of the solvent, and purification of the residue by column chromatography (silica gel, hexane/ethyl acetate, 7:3) to give **11** (3.34 g, 63%) in the form of a colorless oil. $[\alpha]_D = +20.8$ ($c = 1.3$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 5.81$–5.78 (m, 1H), 5.00–4.93 (m, 2H), 3.68–3.60 (m, 2H), 3.61–3.60 (m, 2H), 2.17 (s, 1H), 2.04–2.03 (m, 2H), 1.72–1.71 (m, 3H), 1.52–1.45 (m, 3H), 1.37 (s, 6H), 1.37–1.28 ppm (m and brs, 12H).

(4*R*,5*R*)-1-Iodo-4,5-isopropylidenedioxy-14-pentadecene (12): Iodine (3.42 g, 13.44 mmol) was added to a solution of **11** (3.34 g, 11.2 mmol), PhP_3 (4.42 g, 16.8 mmol), and imidazole (1.15 g, 16.8 mmol) in CH_2Cl_2 (26 mL) at 0°C. The mixture was stirred at RT for 2 h and a saturated solution of $NaHCO_3$ was added, followed by I_2 until the color started appearing. The reaction mixture was worked up with hexanes and water and the organic phase washed with a 10% aqueous $Na_2S_2O_3$ solution. Solvents were removed under vacuum and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 19:1) to give **12** (4.07 g, 89%) as a colorless oil. ^{1}H NMR (300 MHz): $\delta = 5.89$–5.75 (m, 1H), 5.04–4.91 (m, 2H), 3.62–3.60 (m, 2H), 3.25 (t, $J = 6.6$ Hz, 2H), 2.09–2.01 (m, 4H), 1.71–1.44 (m, 4H), 1.39 (s, 6H), 1.39–1.31 ppm (m and brs, 12H); ^{13}C NMR (75 MHz): $\delta = 139.0$, 114.0, 107.9, 80.8, 79.9, 33.9, 33.8, 33.0, 30.2, 29.9, 29.6, 29.5, 29.2, 29.0, 27.5, 27.4, 26.2, 7.1 ppm; ESIMS: *m/z* calcd for $C_{18}H_{33}IO_2$: 408; found: 409 $[M+H]^-$, 431 $[M+Na]^-$, 407 $[M-H]^-$, 443 $[M+Cl]^-$.

(4*R*,5*R*)-4,5-Isopropylidenedioxy-14-pentadecen-1-yl-triphenylphosphonium iodide (6): A mixture of **12** (4.05, 10 mmol), PPh_3 (5.24 g, 20 mmol), and $NaHCO_3$ (1.68 g, 20 mmol) in CH_3CN (120 mL) was heated at reflux for 16 h. Solvents were removed and the residue was redissolved in CH_2Cl_2. Inorganic material was removed by filtration, the solvents were also removed, and the residue was triturated with diethyl ether to afford **6** (5.25 g, 78%) in the form of a thick syrup. ^{1}H NMR (300 MHz): $\delta =$ 7.77–7.72 (m, 9H), 7.68–7.62 (m, 6H), 5.79–5.66 (m, 1H), 4.94–4.81 (m, 2H), 3.75–3.62 (m, 2H), 3.58–3.47 (m, 2H), 2.02–1.93 (m, 2H), 1.86–1.65 (m, 2H), 1.45–1.38 (m, 2H), 1.29 (s, 6H), 1.29–1.20 ppm (m, 14H); ^{13}C NMR (75 MHz): $\delta = 138.8$, 134.8, 134.7, 133.3, 133.2, 130.2, 130.1, 118.1, 117.0, 113.7, 107.7, 80.8, 79.9, 32.6, 32.4, 29.5, 29.3 (×2), 28.9, 28.8, 27.3, 27.2, 26.1 ppm; ESIMS: *m/z* calcd for $C_{36}H_{48}IO_2P$: 670; found: 705 $[M+Cl]^-$.

(*cis*,4*R*,5*R*,12*R*,13*R*)-5-*tert*-Butyldiphenylsilyloxytricos-12,13-isopropylidenedioxy-8,22-dien-1,4-olide (13): NaHMDS (1.0 M in THF, 4.45 mL) was added to a stirred solution of Wittig salt **6** (2.98 g, 4.45 mmol) in dry THF (5 mL) at −78°C and the mixture was stirred at the same temperature for 2 h. HMPA (1.38 mL, 7.94 mmol) and aldehyde **7**[22] in THF was added dropwise, and the mixture was stirred for 16 h at −78°C to RT. Saturated aqueous NH_4Cl was added and the mixture was extracted with Et_2O. The combined organic layer was washed with brine and dried over $MgSO_4$. The crude residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 10:1) affording compound **13** (2.37 g, 73%) in the form of a light yellow oil. $[\alpha]_D = -13.4$ ($c = 1.1$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 7.71$–7.69 (m, 4H), 7.46–7.38 (m, 6H), 5.84–5.77 (m, 1H), 5.26–5.21 (m, 1H), 5.04–4.97 (m, 2H), 4.94–4.92 (m, 1H), 4.53 (dt, $J = 6.6$, 3.7 Hz, 1H), 3.76–3.73 (m, 1H), 3.59–3.51 (m, 2H), 2.58–2.43 (m, 2H), 2.18–2.12 (m, 2H), 2.07–1.88 (m, 6H), 1.71–1.29 (m and brs, 18H), 1.37 (s, 6H), 1.06 ppm (s, 9H); ^{13}C NMR (100 MHz): $\delta = 177.1$, 139.0, 135.8, 135.7, 133.6, 133.0, 129.8, 129.6, 129.4, 129.0, 127.6, 127.5, 114.1, 107.7, 80.7, 80.6, 80.1, 74.4, 33.7, 32.8, 32.7, 32.2, 29.6, 29.4, 29.3, 29.0, 28.8, 28.4, 27.2, 26.9, 26.0, 23.7, 23.2, 22.8, 19.4 ppm; ESIMS: *m/z* calcd for $C_{42}H_{62}SiO_5$: 674; found: 697 $[M+Na]^-$, 673 $[M-H]^-$, 709 $[M+Cl]^-$.

(*cis*,4*R*,5*R*,12*R*,13*R*)-5-Hydroxytricos-12,13-isopropylidenedioxy-8,22-dien-1,4-olide (5): TBAF (1 M in THF, 5.3 mL, 5.3 mmol) was added to a solution of compound **13** (2.36 g, 3.5 mmol) in dry THF (35 mL) at 0°C, and the mixture was stirred for 2 h at RT. Workup using diethyl ether/water followed by purification (silica gel, hexanes/ethyl acetate, 1:1) afforded **5** (1.14 g, 81%) as a colorless oil. $[\alpha]_D = -1.2$ ($c = 1.16$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 5.84$–5.79 (m, 1H), 5.43–5.38 (m, 2H), 5.01–4.92 (m, 2H), 4.41 (dt, $J = 7.3$, 4.8 Hz, 1H), 3.60–3.59 (m and brs, 3H), 2.61–2.52 (m, 2H), 2.28–2.03 (m, 8H), 1.50–1.27 (m and brs, 18H), 1.36 ppm (s, 6H); ^{13}C NMR (100 MHz): $\delta = 177.3$, 139.0, 130.0, 129.0, 113.4, 107.7, 83.0, 80.7, 80.2, 72.5, 33.6, 32.8, 32.4, 29.6, 29.3, 29.2, 28.9, 28.7, 28.5, 27.2, 26.0 (×2), 23.9, 23.8, 23.0 ppm; ESIMS: *m/z* calcd for $C_{26}H_{44}O_5$: 436; found: 459 $[M+Na]^-$, 435 $[M-H]^-$, 471 $[M+Cl]^-$.

(4*R*,5*R*,8*R*,9*S*,12*R*,13*R*)-9-Hydroxy-12,13-isopropylidenedioxy-5,8-oxidotricos-22-en-1,4-olide (14): Re_2O_7 (3.06 g, 6.33 mmol) was added in portions to a solution of compound **5** (0.92 g, 2.11 mmol) and 2,6-lutidine (2.11 mL, 19.0 mmol) in dry CH_2Cl_2 (20 mL). The mixture was stirred overnight at RT and then quenched by dropwise addition of saturated solution of $NaHCO_3$ (8 mL) and H_2O_2 (35% in water, 8 mL). After stirring was continued for 20 min, the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 3:1) to give **14** (0.72 g, 76%) in the form of a colorless oil. $[\alpha]_D = +7.44$ ($c = 1.08$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 5.85$–5.77 (m, 1H), 5.00–4.91 (m, 2H), 4.47–4.44 (m, 1H), 4.09–4.06 (m, 1H), 3.91–3.87 (m, 1H), 3.78–3.76 (m, 1H), 3.61–3.55 (m, 2H), 2.70–2.63 (m, 1H), 2.50–2.43 (m, 2H), 2.32–2.25 (m, 1H), 2.21–2.14 (m, 1H), 2.07–2.00 (m, 3H), 1.96–1.86 (m, 3H), 1.83–1.78 (m, 1H), 1.68–1.61 (m, 1H), 1.53–1.28 (m and brs, 15H), 1.37 ppm (s, 6H); ^{13}C NMR (75 MHz): $\delta = 177.4$, 139.2, 114.1, 108.0, 83.2, 81.4, 81.1, 81.0 (×2), 71.7, 33.8, 32.7, 29.7, 29.6, 29.4, 29.2, 29.0, 28.9, 28.2, 28.0, 27.3, 27.2, 26.1, 25.4, 24.6 ppm; ESIMS: *m/z* calcd for $C_{26}H_{44}O_6$: 452; found: 453 $[M+H]^-$, 451 $[M-H]^-$, 487 $[M+Cl]^-$.

(4*R*,5*R*,8*R*,9*S*,12*R*,13*R*)-12,13-Isopropylidinedioxy-9-mesyloxy-5,8-oxidotricos-22-en-1,4-olide (15): MsCl (0.25 mL, 3.18 mmol) was added to a solution of **14** (0.72 g, 1.59 mmol) and Et_3N (0.89 mL, 6.36 mmol) in CH_2Cl_2 (17 mL) at −30°C. The mixture was stirred at this temperature for 0.5 h, was quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with water and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 7:3) to yield **15** (0.77 g, 91%) in the form of a colorless oil. $[\alpha]_D = +12.4$ ($c = 1.39$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 5.82$–5.77 (m, 1H), 4.98–4.88 (m, 2H), 4.80–4.77 (m, 1H), 4.46–4.42 (m, 1H), 4.07–4.03 (m, 2H), 3.60–3.55 (m, 1H), 3.51 (dt, $J = 8.8$, 2.6 Hz, 1H), 3.02 (s, 3H), 2.61–2.59 (m, 1H), 2.48–2.42 (m, 1H), 2.30–2.23 (m, 1H), 2.14–1.75 (m, 9H), 1.69–1.61 (m, 1H), 1.52–1.44 (m, 4H), 1.33 (s, 6H), 1.33–1.22 ppm (m, 11H); ^{13}C NMR (75 MHz): $\delta =$ 177.2, 139.1, 114.0, 107.9, 83.6, 81.0, 80.9, 80.8, 80.7, 80.5, 38.5, 33.7, 33.7, 32.6, 31.4, 29.6 (×2), 29.3 (×3), 29.0, 28.8 (×2), 28.4, 28.1, 27.7, 27.2 (×4), 26.0 (×3), 24.5 ppm; ESIMS: *m/z* calcd for $C_{27}H_{46}O_8S$: 530; found: 531 $[M+H]^-$, 553 $[M+Na]^-$, 529 $[M-H]^-$, 565 $[M+Cl]^-$.

(4*R*,5*R*,8*R*,9*S*,12*R*,13*R*)-12,13-Dihydroxy-9-mesyloxy-5,8-oxidotricos-22-en-1,4-olide (16): TsOH (0.415 g, 2.18 mmol) was added to a solution of **15** (0.77 g, 1.45 mmol) in MeOH/water (4:1, 8 mL). The mixture was stirred at RT for 16 h, diluted with a saturated solution of $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 1:1) to give the corresponding triol derivative, **16** (0.55 g, 77%) as a light yellow oil. $[\alpha]_D = +7.43$ ($c = 1.74$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 5.84$–5.76 (m, 1H), 4.99–4.90 (m, 2H), 4.83–4.81 (m, 1H), 4.47–4.44 (m, 1H), 4.09–4.04 (m, 2H), 3.38–3.37 (m, 2H), 3.05 (s, 3H), 2.66–2.61 (m, 1H), 2.43 (m, 4H), 2.29–2.26 (m, 1H), 2.08–2.00 (m, 6H), 1.95–1.90 (m, 3H), 1.70–1.68 (m, 2H), 1.49–1.43 (m, 4H), 1.36–1.25 ppm (m and brs, 7H); ^{13}C NMR (75 MHz): $\delta = 177.3$, 139.0, 113.9, 83.9, 81.1, 80.5, 74.3, 38.5, 33.7, 33.5, 29.6, 29.5, 29.4, 29.3, 29.1, 28.9, 28.2, 28.1, 27.8, 26.2, 25.7, 24.6 ppm; ESIMS: *m/z* calcd for $C_{24}H_{42}O_8S$: 490; found: 491 $[M+H]^-$, 513 $[M+Na]^-$, 525 $[M+Cl]^-$.

(4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-13-Hydroxy-5,8,9,12-dioxidotricos-22-en-1,4-olide (4): Compound **16** (0.55 g, 1.12 mmol) was dissolved in pyridine (15.5 mL), and the mixture was heated at reflux for 3 h, cooled to RT, diluted with water, and extracted with EtOAc. The organic layer was first washed with a cold 3 N HCl and then with brine, and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 1:1) to give **4** (0.40 g, 90%) as a colorless oil. $[\alpha]_D = +2.04$ ($c = 0.83$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 5.85$–5.77 (m, 1H), 5.00–4.91 (m, 2H),

4.49–4.45 (m, 1H), 4.09 (dt, J=7.1, 2.3, 1H), 3.91–3.84 (m, 2H), 3.81–3.77 (m, 1H), 3.39–3.36 (m, 1H), 2.70–2.66 (m, 1H), 2.48–2.42 (m, 1H), 2.29–2.24 (m, 2H), 2.05–1.93 (m, 7H), 1.76–1.71 (m, 3H), 1.41–1.35 ppm (m and brs, 14H); ^{13}C NMR (75 MHz): δ=177.3, 138.8, 113.8, 82.6, 82.1, 81.2, 81.1, 80.7, 73.6, 33.5, 33.1, 29.4, 29.2, 29.1, 28.8, 28.6, 28.5, 28.1, 28.0 (x2), 27.5, 25.3, 24.3 ppm; ESIMS: m/z calcd for $C_{23}H_{38}O_5$: 394; found: 395 $[M+H]^-$, 417 $[M+Na]^-$, 393 $[M-H]^-$, 429 $[M+Cl]^-$.

(4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-5,8,9,12-Dioxidotricos-22-en-1,4,13-triol (17): $LiAlH_4$ (77 mg, 2.03 mmol) was added in portions to a stirred solution of **4** (0.40 g, 1.01 mmol) in dry diethyl ether at 0°C, and the mixture was allowed to warm to RT, then refluxed for 2 h, cooled back to RT, diluted with diethyl ether, and worked up by dropwise addition of water. The inorganic material was filtered off and washed with EtOAc, and the combined organic solution was collected. Solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate/MeOH, 1:0–19:1) to give **17** (0.34 g, 85%) in the form of a colorless oil. $[\alpha]_D$=+7.15 (c=1.57 in $CHCl_3$); ^{1}H NMR (500 MHz): δ=5.84–5.78 (m, 1H), 5.00–4.92 (m, 2H), 3.90–3.83 (m, 4H), 3.69–3.64 (m, 2H), 3.47–3.43 (m, 1H), 3.41–3.37 (m, 1H), 2.60 (brs, 3H), 2.04–1.97 (m, 6H), 1.75–1.26 ppm (m and brs, 22H); ^{13}C NMR (100 MHz): δ=139.1, 114.0, 83.1, 82.9, 81.8, 81.7, 73.8, 73.7, 62.5, 33.7, 33.2, 30.0, 29.6, 29.5, 29.3, 29.1 (×2), 28.9 (×2), 28.8, 28.2 (×2), 25.5; ESIMS: m/z calcd for $C_{23}H_{42}O_5$: 398.3; found: 421 $[M+Na]^-$, 397 $[M-H]^-$.

(4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-1-*tert*-Butyldimethylsilyloxy-4,13-di(methoxymethoxy)-5,8,9,12-dioxidotricos-22-ene (18): TBSCl (193 mg, 1.28 mmol) was added to a stirred solution of **17** (0.34 g, 0.85 mmol), diisopropylethylamine (0.45 mL, 2.56 mmol), and DMAP (42 mg, 0.34 mmol) in dry CH_2Cl_2 (15 mL), and the solution was stirred for 6 h at RT. Upon completion of the reaction (by TLC), the mixture was cooled to 0°C, and diisopropylethylamine (1.78 mL, 10.2 mmol) and MOMCl (0.87 mL, 11.44 mmol) were added sequentially. The mixture was stirred for another 12 h, worked up with water and CH_2Cl_2, the combined organic layer was washed with water and dried over $MgSO_4$, and the solvents were removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 4:1) to give **18** (0.511 g, 96%) in the form of a colorless oil. $[\alpha]_D$=+29.5 (c=7.29 in $CHCl_3$); ^{1}H NMR (500 MHz): δ=5.79–5.73 (m, 1H), 4.97–4.88 (m, 2H), 4.79 (dd, J=7.0, 1.5, 2H), 4.64 (dd, J=6.8, 2.4 Hz, 2H), 3.99–3.94 (m, 2H), 3.89 (t, J=6.1 Hz, 2H), 3.61–3.57 (m, 2H), 3.48–3.42 (m, 2H), 3.36 (s, 6H), 2.02–1.87 (m, 6H), 1.80–1.72 (m, 2H), 1.67–1.54 (m, 6H), 1.47–1.23 (m and brs, 14H), 0.86 (s, 9H), 0.01 ppm (s, 6H); ^{13}C NMR (100 MHz): δ= 139.1, 114.0, 96.5, 81.7, 81.6, 81.1 (x2), 79.4, 79.2, 63.0, 55.6, 33.7, 31.1, 29.7, 29.5, 29.4, 29.0, 28.8 (×2), 28.2, 28.1, 27.4, 25.9, 25.5, 18.2, −5.4 ppm; ESIMS: m/z calcd for $C_{33}H_{64}O_7Si$: 600; found: 623 $[M+Na]^-$, 635 $[M+Cl]^-$.

(4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-1-*tert*-Butyldimethylsilyloxy-4,13-di(methoxymethoxy)-5,8,9,12-dioxidotricosan-23-ol (19): A solution of olefin **18** (0.228 g, 0.38 mmol) in THF (4 mL) was treated with 9-BBN (0.5 M in THF, 1.36 mL, 0.68 mmol) at 0°C, and the resulting solution was stirred at RT for 4 h. NaOH (3 M, 0.3 mL, 0.94 mmol) and 30% H_2O_2 (0.07 mL, 0.86 mmol) were added to this solution at 0°C, and stirring was continued for 1 h at RT. The reaction mixture was extracted with diethyl ether, washed with water and brine, dried, and concentrated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 1:1) to give **19** (0.20 g, 87%) in the form of a colorless oil. $[\alpha]_D$=+30.0 (c= 1.47 in $CHCl_3$); ^{1}H NMR (500 MHz): δ=4.82 (d, J=7.0 Hz, 2H), 4.67(d, J=7.0 Hz, 2H), 3.99–3.98 (m, 2H), 3.91 (m and brs, 2H), 3.64–3.61 (m, 4H), 3.47 (m and brs, 2H), 3.39 (s, 6H), 1.93–1.92 (m, 4H), 1.80–1.78 (m, 2H), 1.67–1.53 (m, 8H), 1.45–1.43 (m, 5H), 1.27 (m and brs, 11H), 0.88 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (75 MHz): δ=96.9, 81.8, 81.7, 81.2, 81.1, 79.4, 79.3, 63.0, 55.7, 32.8, 31.1, 29.8, 29.5, 29.5, 29.4, 28.9, 28.3, 28.2, 27.4, 25.9, 25.7, 25.6, 18.3, −5.3 ppm; ESIMS: m/z calcd for $C_{33}H_{66}O_8Si$: 618.4; found: 641 $[M+Na]$, 653 $[M+Cl]^-$.

(4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-1-*tert*-Butyldimethylsilyloxy-4,13-di(methoxymethoxy)-23-(*p*-methoxybenzyloxy)methoxy-5,8,9,12-dioxidotricosane (20): A solution of crude *p*-methoxybenzyloxy-methyl chloride (0.137 mg, 0.74 mmol) in 3.5 mL of CH_2Cl_2 was added dropwise to a cooled (0°C) solution of **19** (0.152 g, 0.245 mmol) and diiospropylethylamine (0.21 mL, 1.23 mmol) in CH_2Cl_2 (14 mL). After the addition was complete, the reaction mixture was allowed to warm to RT and was stirred for 3 h. The reaction mixture was washed with saturated aqueous NH_4Cl and brine, and dried over Na_2SO_4. Solvents were removed, and residue was purified by column Chromatography (silica gel, hexane/ethyl acetate, 4:1) to afford **20** (0.186 g, 90%) as a light yellow oil. $[\alpha]_D$=+26.9 (c=1.79 in $CHCl_3$); ^{1}H NMR (500 MHz): δ=7.28 (d, J=8.8 Hz, 2H), 6.88 (d, J= 8.8 Hz, 2H), 4.83 (d, J=7.0 Hz, 2H), 4.73 (s, 2H), 4.67 (dd, J=7.0 Hz, 2.2, 2H), 4.53 (s, 2H), 4.02–3.98 (m, 2H), 3.93–3.90 (m, 2H), 3.80 (s, 3H), 3.63–3.61 (m, 2H), 3.57 (t, J=6.6 Hz, 2H), 3.51–3.48 (m, 2H), 3.39 (s, 3H), 3.39 (s, 3H), 1.94–1.92 (m, 4H), 1.80–1.79 (m, 2H), 1.63–1.58 (m, 8H), 1.47–1.28 (m, 16H), 0.89 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (100 MHz): δ=159.2, 130.0, 129.5, 113.8, 96.6, 94.3, 81.8, 81.7, 81.1, 81.1, 79.5, 79.3, 68.8, 68.0, 63.1, 55.7, 55.2, 33.5, 31.1, 29.8, 29.7, 29.6, 29.4, 28.9, 28.3, 28.2, 27.4, 26.2, 25.9, 25.6, 18.3, −5.3 ppm.

(4*R*,5*R*,8*R*,9*R*,12*R*,13*R*)-4,13-Di(methoxymethoxy)-23-(*p*-methoxybenzyloxy)methoxy-5,8,9,12-dioxidotricosan-1-ol (21): TBAF (1 M in THF, 0.22 mL, 0.22 mmol) was added to a solution of **20** (0.17 g, 0.22 mmol) in dry THF (2 mL) at 0°C. After the mixture was stirred for 2 h at RT, it was worked up by using diethyl ether and water. The crude product was purified (silica gel, hexane/ethyl acetate, 1:1) affording **21** (138 mg, 95%) as a colorless oil. $[\alpha]_D$=+26.89 (c=1.79 in $CHCl_3$); ^{1}H NMR (500 MHz): δ=7.28–7.26 (m, 2H), 6.89–6.86 (m, 2H), 4.83 (dd, J=6.6, 2.9 Hz, 2H), 4.72 (s, 2H), 4.68 (t, J=6.6 Hz, 2H), 4.53 (s, 2H), 4.05–3.98 (m, 2H), 3.92–3.90 (m, 2H), 3.80 (s, 3H), 3.67–3.64 (m, 2H), 3.57–3.53 (m, 3H), 3.49–3.46 (m, 1H), 3.40 (s, 3H), 3.39 (s, 3H), 1.96–1.91 (m, 5H), 1.79–1.27 ppm (m, 26H); ^{13}C NMR (100 MHz): δ=159.3, 129.8, 129.3, 113.7, 96.7, 96.6, 94.2, 81.7, 81.5, 81.2, 81.2, 79.5, 79.3, 68.8, 68.0, 62.9, 55.8, 55.7, 55.3, 31.2, 29.9, 29.8, 29.7, 29.6, 28.9, 28.4, 28.3, 27.6, 26.4, 25.8 ppm; ESIMS: m/z calcd for $C_{36}H_{62}O_{10}$: 654; found: 655 $[M+H]^-$.

(5*R*,6*R*,9*R*,10*R*,13*R*,14*R*)-1,1-Dibromo-5,14-di(methoxymethoxy)-24-(*p*-methoxybenzyloxy) methoxy-6,9,10,13-dioxidotricos-1-ene (22): A solution of DMSO (0.04 mL, 0.53 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise to a stirred solution of oxalyl chloride (0.15 mL, 0.30 mmol) in CH_2Cl_2 (1.5 mL) at −78°C under Ar. After the mixture was stirred for 30 min at −78°C, a solution of **21** (0.10 g, 0.15 mmol) in CH_2Cl_2 (0.6 mL) was added dropwise, and the mixture was stirred at the same temperature for 1 h. Triethylamine (0.15 mL, 1.07 mmol) was added, and the resulting mixture was gradually warmed to 0°C with stirring and poured into ice-water. The mixture was extracted with diethyl ether. The extracts were sequentially washed with cold HCl solution, sat. $NaHCO_3$ solution, water, and brine. The organic layer was dried over $MgSO_4$ and concentrated to give aldehyde (0.10 g). This compound was employed to the next step without further purification.

Triphenyl phosphine (0.168 g, 0.64 mmol) in CH_2Cl_2 (0.4 mL) was added to a stirried solution of CBr_4 (0.106 g, 0.32 mmol) in CH_2Cl_2 (1.3 mL) at 0°C. After 10 min, triethylamine (0.17 mL, 1.26 mmol) was added. After another 10 min, a solution of the aldehyde (99.69 mg) in CH_2Cl_2 (0.8 mL) was added dropwise at 0°C. The mixture was stirred at 0°C for 16 h, poured into sat. $NaHCO_3$ solution, and then extracted with CH_2Cl_2. The extracts were washed with water and brine, dried on Na_2SO_4, and concentrated. The residue was purified by chromatography (silica gel, hexane/ethyl acetate, 10:1) to afford the dibromide **22** (90.0 mg, 73% from **21**). $[\alpha]_D$=+25.07 (c=4.5 in $CHCl_3$); ^{1}H NMR (500 MHz): δ=7.21–7.20 (m, 2H), 6.82–6.80 (m, 2H), 6.36 (t, J=7.15 Hz, 1H), 4.75 (dd, J=6.6, 1.1 Hz, 2H), 4.66 (s, 2H), 4.59 (dd, J=7.0, 3.0 Hz, 2H), 4.46 (s, 2H), 3.95–3.91 (m, 2H), 3.86–3.82 (m, 2H), 3.73 (s, 3H), 3.50 (t, J=6.6 Hz, 2H), 3.45–3.39 (m, 2H), 3.33 (s, 3H), 3.32 (s, 3H), 2.20–2.07 (m, 2H), 1.97–1.83 (m, 4H), 1.75–1.68 (m, 2H), 1.61–1.21 ppm (m, 22H); ^{13}C NMR (100 MHz): δ=159.2, 138.3, 130.0, 129.5, 113.8, 96.8, 96.6, 94.3, 88.9, 81.7, 81.3, 81.2, 79.4, 78.8, 68.8, 68.0, 55.8, 55.7, 55.2, 31.1, 29.8, 29.7, 29.6, 29.4, 29.3, 29.0, 28.2, 28.0, 26.2, 25.6 ppm; ESIMS: m/z calcd for $C_{37}H_{60}O_9Br_2$: 806; found: 829 $[M+Na]^-$, 805 $[M-H]^-$, 841 $[M+Cl]^-$.

(5*R*,6*R*,9*R*,10*R*,13*R*,14*R*)-5,14-Di(methoxymethoxy)-24-(*p*-methoxybenzyloxy)methoxy-6,9,10,13-dioxidotricosan-1-yne (2): A solution of ethylmagnesium bromide in THF (1.0 M, 0.22 mL, 0.22 mmol) was added dropwise to a stirred solution of **22** (90 mg, 0.11 mmol) in THF (1.0 mL) at 0°C, and then the mixture was stirred at the same temperature for 0.5 h. A saturated solution of NH_4Cl (1.0 mL) was added and the resulting mixture was extracted with diethyl ether. The extracts were washed with water and brine, dried, and concentrated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 4:1) to afford **2** (71 mg, 98%) in the form of a light yellow oil. ^{1}H NMR (500 MHz): δ=

7.28 (d, $J=8.5$ Hz, 2H), 6.89 (d, $J=8.5$ Hz, 2H), 4.83 (dd, $J=6.6$, 2.0 Hz, 2H), 4.73 (s, 2H), 4.69 (dd, $J=15.5$, 6.6 Hz, 2H), 4.54 (s, 2H), 4.04–3.98 (m, 2H), 3.95–3.90 (m, 2H), 3.81 (s, 3H), 3.64–3.60 (m, 1H), 3.58 (t, $J=6.6$ Hz, 2H), 3.49–3.46 (m, 1H), 3.41 (s, 3H), 3.40 (s, 3H), 2.37–2.32 (m, 2H), 1.99–1.92 (m, 5H), 1.81–1.57 (m, 10H), 1.46–1.26 ppm (m, 14H); ^{13}C NMR (100 MHz): $\delta=159.2$, 130.0, 129.5, 113.8, 97.0, 96.7, 94.3, 84.2, 83.3, 81.8, 81.5, 81.3, 81.1, 79.5, 78.2, 68.8, 68.5, 68.0, 55.9, 55.7, 55.3, 31.1, 30.2, 29.8, 29.7, 29.6, 29.5, 28.3, 26.2, 25.6, 14.8 ppm; ESIMS: *m/z* calcd for $C_{37}H_{60}O_9$: 648; found: 671 $[M+Na]^-$.

(2*R*)-Oct-7-en-1,2-diol (24): AD-mix-β (141 g) was added to a mixture of 1,7-octadiene (11.1 g, 100 mmol) in *t*BuOH/water (2:1, 570 mL) at 0 °C and the mixture was stirred at this temperature for 18 h. The mixture was worked up by the slow addition of $Na_2S_2O_5$ (47 g), diluted with water and extracted with EtOAc. Solvents were removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:1) to give **24** (4.85 g, 34 %) in the form of a colorless oil. ^{1}H NMR (300 MHz): $\delta=5.90$–5.85 (m, 1H), 5.02–4.91 (m, 2H), 3.67–3.62 (m, 1H), 3.62 (d, $J=11.3$ Hz, 1H), 3.39 (dd, $J=10.6$, 8.1 Hz, 1H), 2.76 (brs, 2H), 2.02 (q, $J=6.7$ Hz, 2H), 1.45–1.25 ppm (m and brs, 6H); ^{13}C NMR (75 MHz): $\delta=138.6$, 114.4, 72.2, 66.8, 33.7, 33.1, 28.9, 25.1 ppm; ESIMS: *m/z* calcd for $C_8H_{16}O_2$: 144.12; found: 145 $[M+H]^-$, 167 $[M+Na]^-$, 143 $[M-H]^-$.

(2*R*)-1-Tosyloxyoct-7-en-2-ol (25): TsCl (2.76 g, 14.5 mmol) was added to a solution of **24** (1.5 g, 10.4 mmol), 2,4,6-collidine (11.88 g, 93.6 mmol), and DMAP (1.26 g, 10.4 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C. The mixture was stirred between 0 °C and RT for 16 h, and then diluted with water and extracted with CH_2Cl_2. The combined organic layer was washed with dilute HCl and then with water, and dried over anhydrous $MgSO_4$. Solvents were evaporated under vacuum and the resultant residue was purified by column chromatography (silica gel, benzene/EtOAc, 9:1) affording **25** (2.1 g, 65 %) in the form of a colorless oil. $[\alpha]_D=-4.1$ ($c=0.35$ in $CHCl_3$); ^{1}H NMR (300 MHz): $\delta=7.79$ (d, $J=8.1$ Hz, 2H), 7.35 (d, $J=8.1$ Hz, 2H), 5.82–5.71 (m, 1H), 5.02–4.92 (m, 2H), 4.05 (dd, $J=9.6$, 2.7 Hz, 1H), 3.92–3.84 (m, 2H), 2.47 (s, 3H), 2.04–2.0 (m,3H), 1.47–1.31 ppm (m and brs, 6H); ESIMS: *m/z* calcd for $C_{15}H_{22}O_4S$: 298; found: 297 $[M-H]^-$, 333 $[M+Cl]^-$.

(2*R*)-1-Tosyloxy-2-*tert*-butyldimethylsilyloxyoct-7-ene (26): TBSOTf (2.12 g, 8.0 mmol) was added to a solution of **25** (2 g, 6.7 mmol) and 2,6-lutidine (1.07 g, 10.1 mmol) in dry CH_2Cl_2 (25 mL) at −78 °C. The mixture was stirred at the same temperature for 1.5 h, then worked up with water and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to give **26** (2.65 g, 96 %) in the form of colorless oil. $[\alpha]_D=+3.0$ ($c=0.45$ in $CHCl_3$); ^{1}H NMR (300 MHz): $\delta=7.76$ (d, $J=8.1$ Hz, 2H), 7.31 (d, $J=8.1$ Hz, 2H), 5.82–5.66 (m, 1H), 4.99–4.83 (m, 2H), 3.88–3.79 (m, 3H), 2.44 (s, 3H), 2.05–1.95 (m, 2H), 1.45–1.22 (m and brs, 6H), 0.82 (s, 9H), 0.11 (s, 3H), 0.04 ppm (s, 3H); ^{13}C NMR (75 MHz): $\delta=144.6$, 138.4, 132.8, 129.6, 127.7, 114.4, 73.0, 69.9, 33.9, 33.6, 28.8, 25.7, 24.3, 21.6, 18, −4.5 −4.7 ppm; ESIMS: *m/z* calcd for $C_{21}H_{36}O_4SSi$: 412; found: 435 $[M+Na]^-$, 447 $[M+Cl]^-$.

(2*R*)-2-*tert*-Butyldimethylsilyloxy-1-iodooct-7-ene (27): A mixture of **26** (2.62 g, 6.26 mmol), NaI (9.54 g, 63.6 mmol) and $NaHCO_3$ (0.53 g, 6.36 mmol) in dry acetone (80 mL) was stirred at reflux temperature for 38 h. Solvent was removed under reduced pressure and the residue was dissolved in water and extracted with EtOAc. The organic layer was washed with aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to afford **27** (2.2 g, 95 %) in the form of a colorless oil. $[\alpha]_D=+7.0$ ($c=0.85$ in $CHCl_3$); ^{1}H NMR (300 MHz): $\delta=5.78$–5.66 (m, 1H), 4.96–4.84 (m, 2H), 3.49–3.44 (m, 1H), 3.11 (d, $J=5.4$ Hz, 2H), 1.98 (q, $J=7.2$ Hz, 2H), 1.55–1.16 (m, 6H), 0.83 (s, 9H), 0.09 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (75 MHz): $\delta=138.6$, 114.4, 71.4, 36.8, 33.7, 28.9, 25.9, 24.5, 18.2, 14.1, −4.2, −4.5 ppm; ESIMS: *m/z* calcd for $C_{14}H_{29}IOSi$: 368.33; found: 369 $[M+H]^-$, 403 $[M+Cl]^-$.

(2*RS*,4*S*,2′*R*)-2-(2′-*tert*-Butyldimethylsilyloxyoct-7′-en-1′-yl)-2-(phenylsulfanyl)pentan-1,4-olide (29): Lactone **28**[34] (1.1 g, 5.29 mmol) in dry THF (5 mL) was added dropwise to an ice-cold solution of LDA (5.8 mmol, prepared from 5.8 mmol *n*BuLi and 6.3 mmol diiso*p*ropylamine in 20 mL dry THF). The mixture was stirred for 30 min, iodide **27** (2.12 g, 5.8 mmol) and HMPA (2.9 g, 2.8 mL, 16 mmol) in THF (5 mL) were added and the mixture was stirred at RT for 20 h. The mixture was worked up with saturated aqueous NH_4Cl and diethyl ether, the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, hexanes/diethyl ether, 1:0–9:1) to give **29** (1.2 g, 50 %) in the form of a colorless oil (mixture of two diastereomers). ^{1}H NMR of the major product (300 MHz): $\delta=7.54$, −7.49 (m, 2H), 7.34–7.27 (m, 3H), 5.78–5.66 (m, 1H), 4.98–4.88 (m, 2H), 4.50–4.40 (m, 1H), 4.25–4.21 (m, 1H), 3.02 (dd, $J=14.1$, 7.5 Hz, 1H), 2.05–1.76 (m, 5H), 1.45–1.19 (m and brs, 9H), 0.89 (d, $J=6.4$ Hz, 3H), 0.88 (s, 9H), 0.13 (s, 3H), 0.10 ppm (s, 3H); ESIMS: *m/z* calcd for $C_{25}H_{40}O_3SSi$: 448.73; found: 471 $[M+Na]^-$, 483 $[M+Cl]^-$.

(4*S*,2′*R*)-2-(2′-*tert*-Butyldimethylsilyloxy-oct-7′-en-1′-yl)pent-2-en-1,4-olide (30): *m*-CPBA (0.77 g, 75 %, 3.35 mmol) was added in portions to a solution of **29** (1.0 g, 2.23 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C. The mixture was stirred at this temperature for 20 min, then worked up with a saturated solution of $NaHCO_3$ and CH_2Cl_2; the combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The residue was dissolved in toluene (30 mL) and heated at the reflux temperature for 2 h; solvents were removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexanes/diethyl ether, 9:1–7:3) to give **30** (0.56 g, 75 %) in the form of a colorless oil. $[\alpha]_D=+16.0$ ($c=0.9$ in $CHCl_3$); ^{1}H NMR (300 MHz): $\delta=$ 7.10 (s, 1H), 5.82–5.68 (m, 1H), 4.99–4.87 (m, 2H), 3.94 −388 (m, 1H), 2.41 (d, $J=5.6$ Hz, 2H), 2.02 (q, $J=7.5$ Hz, 2H), 1.42–1.22 (m and brs, 9H), 0.85 (s, 9H), 0.23 (s, 3H), 0.08 ppm (s, 3H); ^{13}C NMR (75 MHz): $\delta=173.5$, 151.2, 138.4, 130.4, 114.1, 69.9, 36.6, 33.5, 32.6, 28.8, 25.7, 24.5, 18.9, 17.9, −4.5 ppm; ESIMS: *m/z* calcd for $C_{19}H_{34}O_3Si$: 338; found: 361 $[M+Na]^-$, 337 $[M-H]^-$.

(4*S*,2′*R*)-2-(2′-*tert*-Butyldimethylsilyloxyhept-7′-al-1′-yl)pent-2-en-1,4-olide (31): OsO_4 (0.25 g, 1 mmol) was added to a solution of **30** (0.26 g, 0.77 mmol) in THF/water (4:1, 16 mL) under argon. The mixture was stirred for 5 min, and sodium periodate (0.83 g, 3.9 mmol) was added over a 10 min in three portions. The mixture was stirred for 3 h and then diluted with diethyl ether (30 mL) and water (25 mL). The aqueous phase was extracted with additional diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes/diethyl ether, 7:3–3:7) to provide **31** (0.185 g, 71 %) in the form of a colorless oil. ^{1}H NMR (300 MHz): $\delta=9.71$ (t, $J=1.8$ Hz, 1H), 7.07 (s, 1H), 4.99 (q, $J=6.8$ Hz, 1H), 3.95–3.88 (m, 1H), 2.42 −2.36 (m, 4H), 1.61 −1.17 (m, brs, 9H), 0.84 (s, 9H), 0.12 (s, 3H), 0.04 ppm (s, 3H); ESIMS: *m/z* calcd for $C_{18}H_{32}O_4Si$: 340.56; found: 339 $[M-H]^-$.

(4*S*,2′*R*)-2-(2′-*tert*-Butyldimethylsilyloxy-8′-iodooct-7′-en-1-yl)pent-2-en-1,4-olide (3): A mixture of aldehyde **31** (110 mg, 0.32 mmol) and iodoform (260 mg, 0.66 mmol) in dry THF (5 mL) was added dropwise to a solution of $CrCl_2$ (240 mg, 1.94 mmol) in dry THF (3 mL) at 0 °C and stirred for 4 h at the same temperature. The reaction was quenched by addition of water and extracted with diethyl ether. The combined diethyl ether layer was washed with brine, dried over $MgSO_4$, and evaporated to a residue which was chromatographed over (silica gel, hexanes/EtOAc, 9:1) to yield iodide **3** (90 mg, 60 %) as a mixture of *trans* and *cis* isomers (5:4) in the form of an oil. ^{1}H NMR (300 MHz): $\delta=7.10$ (d, $J=1.5$, 1H), 6.53–6.44(m, 1H), 5.82–5.68 (m, 1H), 4.99–4.87 (m, 2H), 3.94–388 (m, 1H), 2.41 (d, $J=5.6$ Hz, 2H), 2.02 (q, $J=7.5$ Hz, 2H), 1.42–1.22 (m and brs, 9H), 0.85 (s, 9H), 0.28 (s, 3H), 0.11 ppm (s, 3H); ESIMS: *m/z* calcd for $C_{19}H_{33}IO_3Si$: 464.95; found: 487 $[M+Na]^-$, 463 $[M-H]^-$, 499 $[M+Cl]^-$.

{9(*E*,*Z*)}-4-*tert*-Butyldimethylsilyloxy-15,24-di(methoxymethoxy)-34-(*p*-methoxybenzyloxy)methyoxyasimicin-9-en-11-yne (32): To a stirred solution of **2** (54.3 mg, 83 μmol) and vinyl iodide **3** (65.3 mg, 141 μmol) in Et_3N (1.6 mL) were added $(Ph_3P)_2PdCl_2$ (5.9 mg, 8.4 μmol) and CuI (5.1 mg, 26.8 μmol) at room temperature, and the reaction mixture was stirred at room temperature for 2 h and poured into ice-water. The resulting mixture was extracted with ethyl acetate. The extracts were washed sequentially with cold HCl (10 %) solution, water, saturated $NaHCO_3$ solution, water, and brine. Organic layer was dried and concentrated, and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 2:1) to give compound **32** (89.5 mg, 83 %) as a stereoisomeric mixture. ^{1}H NMR (500 MHz): $\delta=7.28$ (d, $J=8.8$ Hz, 2H), 7.12 (brs, 1H), 6.88 (d, $J=8.8$ Hz, 2H), 6.05–5.99 (m, 1H), 5.43 (d, $J=$

15.8 Hz, 1H), 5.01 (dd, J=13.0, 6.0 Hz, 1H), 4.83 (d, J=6.6 Hz, 2H), 4.73 (s, 2H), 4.69 (dd, J=16.3, 6.8 Hz, 2H), 4.53 (s, 2H), 4.03–3.89 (m, 5H), 3.81 (s, 3H), 3.62–3.60 (m, 1H), 3.57 (t, J=6.6, 2H), 3.48–3.46 (m, 1H), 3.40 (s, 3H), 3.40 (s, 3H), 2.46–2.40 (m, 4H), 2.07–2.05 (m, 2H), 1.97–1.92 (m, 4H), 1.77–1.72 (m, 4H), 1.69–1.57 (m, 6H), 1.42–1.25 (m, 23H), 0.88 (s, 9H), 0.05 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (100 MHz): δ=173.9, 159.1, 151.5, 143.1, 142.3, 130.6, 129.9, 129.4, 113.7, 109.9, 96.8, 96.6, 94.2, 88.0, 81.7, 81.5, 81.2, 81.1, 79.4, 78.4, 77.4, 69.9, 68.8, 67.9, 55.8, 55.6, 55.2, 36.6, 32.8, 32.6, 31.1, 30.4, 29.9, 29.7, 29.6, 29.5, 29.4, 28.8, 28.2, 26.2, 25.8, 25.5, 24.5, 18.9, 17.9, 15.7, −4.5 ppm; ESIMS: *m/z* calcd for $C_{56}H_{92}O_{12}Si$: 984.6; found: 1007.6 $[M+Na]^-$, 983.4 $[M-H]^-$, 1019.4 $[M+Cl]^-$.

4-*tert*-Butyldimethylsilyloxy-15,24-di(methoxymethoxy)-34-(*p*-methoxybenzyloxymethoxy)asimicin (33): A mixture of **32** (89.5 mg, 91 μmol) and tris(triphenylphosphine)rhodium chloride (65 mg, 70 μmol) in benzene/methanol (1:1, 14 mL) was stirred at room temperature for 16 h under hydrogen atmosphere and concentrated, The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 1:1) to give **33** (81.2 mg, 90%) as a colorless oil. $[\alpha]_D$=+29.47 (c=0.57 in $CHCl_3$); ^{1}H NMR (500 MHz): δ=7.28 (d, J=8.45 Hz, 2H), 7.13 (brs, 1H), 6.89 (d, J=8.45 Hz, 2H), 5.01–5.00 (m, 1H), 4.83 (d, J=6.95 Hz, 2H), 4.73 (s, 2H), 4.68 (d, J=6.6 Hz, 2H), 4.54 (s, 2H), 4.03–3.98 (m, 2H), 3.97–3.91 (m, 3H), 3.81 (s, 3H), 3.58 (t, J=6.6 Hz, 2H), 3.48 (m, 2H), 3.40 (s, 6H), 2.43 (d, J=5.5 Hz, 2H), 1.93–1.92 (m, 4H), 1.78 (m, 2H), 1.68–1.57 (m, 6H), 1.47–1.26 (m, 37H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (100 MHz): δ=174.0, 159.1, 151.4, 130.7, 129.9, 129.4, 113.7, 96.6, 94.2, 81.6, 81.1, 79.4, 77.4, 70.1, 68.8, 68.0, 55.6, 55.2, 36.9, 32.6, 31.1, 29.7, 29.6, 29.5, 29.4, 28.2, 26.2, 25.8, 25.5, 25.0, 18.9, 18.0, −4.5 ppm; ESIMS: *m/z* calcd for $C_{56}H_{98}O_{12}Si$: 990.68; found: 1014 $[M+Na]^-$, 990 $[M-H]^-$, 1026 $[M+Cl]^-$.

4-*tert*-Butyldimethylsilyloxy-15,24-di(methoxymethoxy)-34-hydroxyasimicin (34): DDQ (24 mg, 106 μmol) was added to a solution of ether **33** (69.8 mg, 70.5 μmol) in H_2O/CH_2Cl_2 (1:10, 1.3 mL). Saturated $NaHCO_3$ was added after 1 h, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried and concentrated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate, 1:1–0:1) to give **34** (54.7 mg, 92%) as a colorless oil. $[\alpha]_D$=+29.7 (c=2.7 in $CHCl_3$); ^{1}H NMR (500 MHz): δ=7.13 (d, J=1.1 Hz, 1H), 5.03–5.00 (m, 1H), 4.83 (dd, J=6.8, 2.0 Hz, 2H), 4.68 (d, J=6.6 Hz, 2H), 4.02–3.91 (m, 5H), 3.64 (t, J=6.6 Hz, 2H), 3.49–3.46 (m, 2H), 3.40 (s, 6H), 2.43 (d, J=5.5 Hz, 2H), 1.95–1.91 (m, 4H), 1.81–1.74 (m, 2H), 1.66–1.55 (m, 10H), 1.47–1.26 (m, 33H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (100 MHz): δ=174.0, 151.5, 130.8, 96.6, 81.7, 81.6, 81.2, 79.4, 77.4, 70.1, 63.0, 55.7, 36.9, 32.7 (×2), 31.1, 29.8, 29.7 (×2), 29.6, 29.5 (×2), 29.4, 28.2, 25.8, 25.7, 25.6, 25.5, 25.1, 18.9, 18.0, −4.5 ppm; ESIMS: *m/z* calcd for $C_{47}H_{88}O_{10}Si$: 840.6; found: 842 $[M+H]^-$, 864 $[M+Na]^-$, 840 $[M-H]^-$, 876 $[M+Cl]^-$.

34-Hydroxyasimicin (1b): $BF_3{\cdot}Et_2O$ (0.08 mL, 0.654 μmol) was added dropwise to a solution of **34** (9.2 mg, 10.9 μmol) in dimethyl sulfide (0.5 mL) at 0°C, the mixture as stirred for 1 h, quenched with saturated $NaHCO_3$, and then diluted with EtOAc. The mixture was then washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/methanol, 20:1–10:1) to give **1b** (4.7 mg, 68%) as a colorless oil. $[\alpha]_D$=+15.2 (c=0.33 in CH_3OH); ^{1}H NMR (500 MHz, [D$_4$]methanol): δ=7.35 (dd, J=2.8, 1.3 Hz, 1H), 5.11–5.07 (m, 1H), 3.87–3.83 (m, 4H), 3.79–3.77 (m, 1H), 3.54 (t, J=6.6 Hz, 2H), 3.41–3.3.37 (m, 2H), 2.43–2.39 (m, 1H), 2.35–2.31(m, 1H), 1.99–1.95 (m, 4H), 1.74–1.63 (m, 4H), 1.54–1.42(m, 10H), 1.41–1.39 (m, 3H), 1.36–1.29 ppm (m, 28H); ^{13}C NMR (125 MHz, [D$_4$]methanol): δ=176.6, 154.5, 131.7, 84.4, 83.6, 79.9, 75.0, 70.6, 63.2, 38.5, 34.5, 34.1, 33.8, 31.0, 30.9, 30.8, 29.9, 29.4, 27.1 (×2), 26.9, 19.3 ppm; HRMS: *m/z*: calcd for $C_{37}H_{66}O_8Na$: 661.4655; found: 661.4629 $[M+Na]^-$.

Asimicin-34-yl 3-(4-benzoylphenyl)propionate (1c): A mixture of **34** (10 mg, 11.89 μmol), 3-(4-benzoylphenyl)propionate (6.0 mg, 23.78 μmol), and DMAP (0.43 mg, 3.57 μmol) in CH_2Cl_2 (0.3 mL) was treated at 0°C with EDCI (2.7 mg, 14.27 μmol). The reaction mixture was stirred at room temperature for 16 h, quenched with water, and extracted with Et_2O. The organic layer was washed with 1N HCl, water, and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 2:1) to give **35** (14.4 mg, 98%) as a light yellow oil. $[\alpha]_D$=+21.4 (c=0.96 in $CHCl_3$); ^{1}H NMR (500 MHz): δ=7.80–7.75 (m, 4H),7.61–7.57 (m, 1H), 7.50–7.47 (m, 2H), 7.34–7.32 (m, 2H), 7.13 (d, J=1.1 Hz, 1H), 5.02–5.00 (m, 1H), 4.83 (dd, J=7.0, 1.5 Hz, 2H), 4.68 (d, J=6.6 Hz, 2H), 4.08 (t, J=6.8 Hz, 2H), 4.02–3.90 (m, 5H), 3.49–3.48 (m, 2H), 3.40 (s, 6H), 3.05 (t, J=7.7 Hz, 2H), 2.68 (t, J=6.6 Hz, 2H), 2.43–2.42 (m, 2H), 1.95–1.92 (m, 3H), 1.78–1.75 (m, 2H), 1.65–1.60 (m, 12H), 1.46–1.41 (m, 10H), 1.26 (m, 22H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR(100 MHz): δ=200.8, 178.5, 177.1, 155.9, 150.1, 142.2, 140.1, 136.7, 135.3, 134.9, 134.4, 132.7 (×2), 101.1, 86.2, 85.7, 84.0, 81.8, 74.6, 69.3, 60.2, 41.4, 39.8, 37.2, 36.4, 35.6, 35.4, 34.3, 34.2, 34.0 (x3), 33.7, 33.5, 33.1, 32.7, 30.4, 30.3, 30.1, 29.6, 23.4, 22.5, −4.5 ppm; ESIMS: *m/z* calcd for $C_{63}H_{100}O_{12}Si$: 1076.7; found: 1100 $[M+Na]^-$, 1076 $[M-H]^-$, 1112 $[M+Cl]$.

$BF_3{\cdot}Et_2O$ (58 μL) was added to a solution of **35** (8.4 mg, 7.7 μmol) in methylsulfide (0.45 mL) at 0°C, and the mixture was stirred at this temperature for 1 h. After addition of saturated $NaHCO_3$ solution, the resulting mixture was extracted with EtOAc. The organic phase was washed with water and brine and dried in Na_2SO_4. This crude residue was purified by column chromatography (silica gel, ethyl acetate/MeOH, 10:1) to give **1c** (5.0 mg, 74%) as a colorless oil. $[\alpha]_D$=+8.9 (c=0.27 in $CHCl_3$); ^{1}H NMR (500 MHz): δ=7.80–7.75 (m, 4H), 7.60–7.58 (m, 1H), 7.50–7.47 (m, 2H), 7.33–7.32 (m, 2H), 7.19 (d, J=1.1 Hz, 1H), 5.08–5.04 (m, 1H), 4.07 (t, J=6.7 Hz, 2H), 3.89–3.82 (m, 5H), 3.39 (brs, 2H), 3.05 (t, J=7.7 Hz, 2H), 2.70 (t, J=7.7 Hz, 2H), 2.55–2.51(m, 1H), 2.45 (brs, 2H), 2.43–2.38 (m, 1H), 2.30 (brs, 1H), 2.00–1.98 (m, 4H), 1.71–1.59 (m, 12H), 1.44–1.27 ppm (m, 33H); ^{13}C NMR (125 MHz): δ=196.4, 174.6, 172.6, 151.8, 145.6, 137.7, 135.7, 132.3, 131.2, 130.5, 130.0, 128.3, 83.2, 81.8, 78.0, 74.1, 70.0, 64.8, 37.4, 35.4, 33.4, 33.3, 30.9, 29.7 (×2), 29.6, 29.5, 29.2, 30.0, 28.6, 28.4, 25.9, 25.6 (×3), 19.1 ppm; HRMS calcd for $C_{53}H_{78}O_{10}Na$: 897.5487; found: 897.5457 $[M+Na]^-$.

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