Enantioselective Total Synthesis of (+)-Scyphostatin, a Potent and Specific Inhibitor of Neutral Sphingomyelinase

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Abstract: The total synthesis of (+)-scyphostatin, a specific and potent neutral sphingomyelinase inhibitor from a microorganism, was accomplished for the first time starting from D-arabinose and both enantiomers of methyl 3-hydroxy-2-methylpropionate. The method involves (a) stereoselective aldol coupling of a methyl 1,3-dioxolane-4-carboxylate with the Garner aldehyde to establish the asymmetric quaternary carbon center at C4, (b) ring-closing metathesis of the resultant diene to construct the cyclohexene ring, (c) Negishi coupling of a vinyl iodide and an alkyl iodide to form the requisite trisubstituted *E*-alkene, (d) formation of an amide from the cyclohexene segment and the trisubstituted *E*-alkene fatty acid segment, and (e) stereospecific formation of an epoxide ring from the mesylate of the amide formed from the two segments.

Key words: scyphostatin, sphingomyelinase, inhibitors, total synthesis, aldol reaction, Negishi coupling

Introduction

Scyphostatin (**1**, Figure 1), isolated from the mycelia extract *Trichopeziza mollissima* SANK 13892 by Ogita et al. in 1997, has been shown to be a powerful and specific inhibitor of membrane-bound neutral sphingomyelinase (N-SMase).[1,2] It has been reported that **1** inhibits N-SMase and acidic SMase (A-SMase) with IC_{50} values of 1.0 μM and 49.3 μM, respectively.[1,2] Remarkably, of the many low-molecular-weight N-SMase inhibitors of natural[3] or synthetic[4] origin, this natural product is the most potent and specific one known to date.

SMase is the enzyme that specifically cleaves the phosphoester linkage of sphingomyelin (SM) to generate phosphocholine and ceramide. The SM-derived ceramide has been known as an intracellular lipid second messenger in mammalian cell membranes and plays important roles in the cellular signal transmission pathway, in particular, as a signal transduction factor in cell differentiation and apoptosis induction.[5] Consequently, SMase inhibitors are considered as valuable chemical tools to explore the biological function of the enzyme and the catabolite ceramide in signal transduction. Additionally, potent and selective SMase inhibitors are highly anticipated to be promising candidates for the treatment of ceramide-mediated pathogenic states such as AIDS,[6] inflammation,[7] and immunological and neurological disorders.[8]

The gross structure of scyphostatin (**1**) was revealed by extensive spectroscopic analyses and derivatization studies.[1] It consists of a novel, highly oxygenated cyclohexenone ring attached to an aminopropanol side chain substituted with a 20-carbon unsaturated fatty acid. This initial structure elucidation only established the relative and absolute stereochemistry of the cyclohexenone portion of **1**. Subsequently, Kogen et al. determined the relative and absolute configurations of the three stereogenic centers at C8′, C10′, and C14′ in the fatty acid side chain.[9] At almost the same time, Hoye et al. achieved an enantioselective synthesis of the 20-carbon unsaturated fatty acid moiety for the first time, and provided alternative proof of its stereostructure, including the absolute configuration.[10]

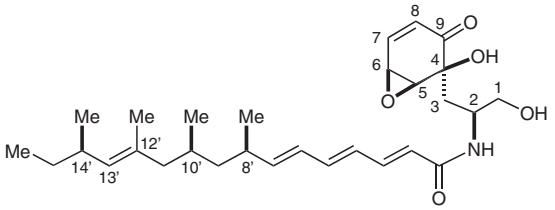

Figure 1 Structure of (+)-scyphostatin (**1**)

The remarkable biological properties and unique structural features have made **1** an exceptionally intriguing and timely target for total synthesis. So far, many synthetic efforts toward scyphostatin (**1**) have been reported.[11] We have already reported our own preliminary results concerning the enantioselective synthesis of the epoxycyclohexenone substructure.[12] Subsequently, we have also disclosed an efficient method for the introduction of a fatty acid side chain at the aminopropanol moiety.[13] More recently, we have communicated the first total synthesis of (+)-scyphostatin (**1**) in an enantiomerically pure form.[14] In this article, we wish to describe the full details of our successful total synthesis of (+)-**1**.

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Results and Discussion

Synthetic Plan for (+)-Scyphostatin (1)

Our synthetic plan for (+)-scyphostatin (**1**), outlined in Scheme 1, is based on our intensive model studies.[12] Since the highly oxygenated cyclohexenone system in **1** was expected to be fairly labile under acidic and/or basic conditions,[1,2] we planned the construction of the epoxycyclohexenone system to be at a late stage of the synthesis. The target molecule **1** would be produced from the cyclohexenone segment **2** and the 20-carbon fatty acid segment **3** via an amide coupling of these segments, followed by enone and epoxide-ring formations.

The segment **2** would be derived from diene **4** through ring-closing metathesis (RCM). The RCM substrate **4** would be prepared through aldol coupling of ester **5** with the Garner aldehyde (**6**),[15] where we envisioned that **6** approaches exclusively from the less hindered α-face of the enolate of **5**, leading to establishment of the requisite asymmetric quaternary carbon center at the C4-position (scyphostatin numbering). This type of coupling reaction is considerably challenging at the synthetic chemistry level, because substrate **5** possesses unusual trihydroxy functionalities at the C4-, C5-, and C6-positions. Ester **5**, in turn, could be accessible from D-arabinose (**7**) that has the correct stereochemistries for **5**.

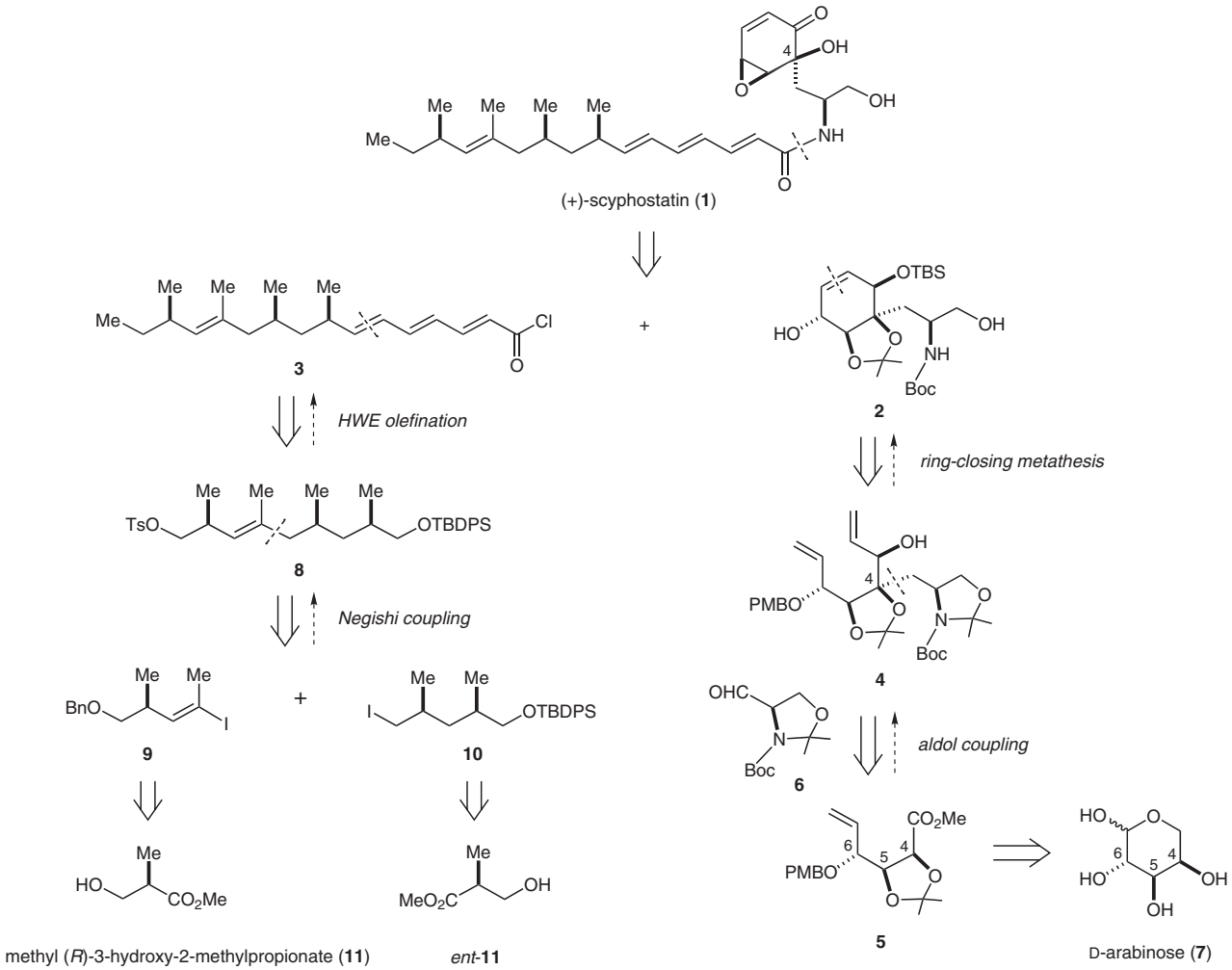
On the other hand, segment **3** could be derived from the Hoye intermediate **8**[10] through Horner–Wadsworth–Emmons (HWE) olefination. The key feature of our synthesis of **8** is Negishi coupling between vinyl iodide **9** and alkyl iodide **10** to generate the requisite trisubstituted *E*-olefin **8**. Intermediates **9** and **10** could be accessed from the two commercially available isomers methyl (*R*)-3-hydroxy-2-methylpropionate (**11**) and its *S*-isomer *ent*-**11**, respectively.

Biographical Sketches

Munenori Inoue was born in 1971 in Hiroshima, Japan. He received his PhD in 1999 from the University of Tokyo under the direction of Prof. Takeshi Kitahara. After spending a postdoctoral year (1999–2001) with Prof. John L. Wood at Yale University, he joined the group of Prof. Tadashi Katoh at Sagami Chemical Research Center as a research fellow (2001–2004). In 2004 he became a junior research fellow and started his own research at the same institute. He is also a visiting associate professor at the Tokyo Institute of Technology. His current research interests include the synthesis of biologically active compounds, especially natural products, and the development of new chemical reactions.

Wakako Yokota was born in 1975 in Kochi, Japan. She studied pharmaceutical science at Tokushima University and obtained her BS degree in 1999 and MS degree in 2001 under the guidance of Prof. Kozo Shishido. In 2001 she joined the group of Prof. Tadashi Katoh at Sagami Chemical Research Center as a research fellow (2001–2003). In 2003 she was transferred to the group of Dr. Kenji Hirai at the same institute, where she was engaged in the synthesis of new agrochemicals (2003–2006). Currently she works as a pharmacist at Kitasato Pharmacy in Kanagawa, Japan.

Tadashi Katoh received his PhD in 1988 from Hoshi University under the direction of Prof. Toshio Honda and the late Prof. Tetsuji Kametani. After spending a postdoctoral year (1988–1989) with Prof. Philip D. Magnus at Indiana University and the University of Texas, he joined Sagami Chemical Research Center as a research fellow in 1989, where he enjoyed working with Dr. Shiro Terashima (1989–1998). In 1998 he was appointed as a visiting professor at the Tokyo Institute of Technology, and started his independent research career. He received a Progress Award (1998) and a Pfizer Award (1999) in synthetic organic chemistry in Japan. In 2004 he moved to Tohoku Pharmaceutical University as full professor. His research interests include development of new synthetic methodologies for structurally unique and biologically significant natural products.



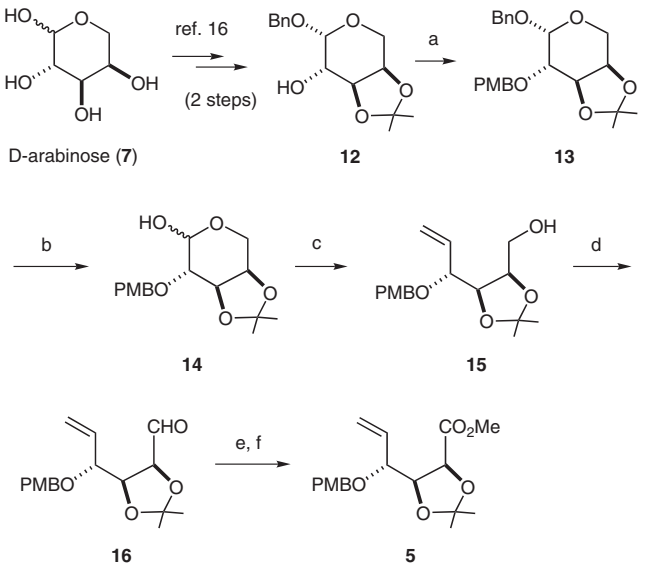
Scheme 1 Synthetic plan for (+)-scyphostatin (**1**)

Synthesis of Methyl Ester 5

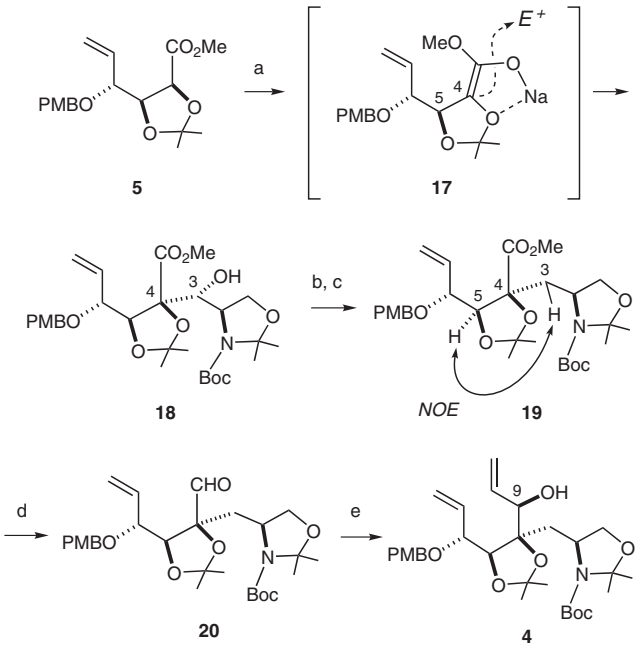
At first, we pursued the synthesis of methyl ester **5** (Scheme 2), the substrate for the crucial aldol coupling reaction, starting from the known compound **12**,[16] readily derived from D-arabinose (**7**) by *O*-benzylglycosylation and acetonide formation. After *p*-methoxybenzyl protection of the hydroxy group in **12** (70% yield), the benzyl protecting group of the resulting ether **13** was removed by hydrogenolysis to furnish hemiacetal **14** (2:1 mixture of α-and β-anomers) in 86% yield. Wittig olefination of **14** afforded alcohol **15** (86% yield), which was further converted into substrate **5** in 74% overall yield over a three-step sequence involving Swern oxidation, oxidation with sodium chlorite, and methyl esterification with diazomethane.

Synthesis of Diene 4

Having obtained intermediate **5**, we next carried out the synthesis of diene **4**, the substrate for the key RCM reaction, as shown in Scheme 3. Initial attempts to achieve the aldol coupling between **5** and the Garner aldehyde (**6**)[15] with a lithium base such as lithium diisopropylamide or lithium hexamethyldisilazide proved to be problematic: the reaction rate was very slow and the yield of the coupling product **18** was low (ca. 30%). After several experiments, we were delighted to find that the use of a sodium base such as sodium hexamethyldisilazide was fairly effective for this coupling reaction. Thus, treatment of **5** with sodium hexamethyldisilazide (1.2 equiv) in tetrahydrofuran at –78 °C, followed by reaction with the Garner aldehyde (**6**) (1.1 equiv) at the same temperature for four hours provided the desired coupling product **18** in 69% yield as a single diastereomer. The newly formed C4 stereochemistry of the product **18** was completely controlled, as we expected; the assignment was later confirmed by an NOESY experiment of the transformed compound **19**. The C3 stereochemistry in **18** was tentatively assigned on the basis of the well-known Felkin–Anh model. As shown in intermediate **17** (Scheme 3), the electrophile **6** (E^+) would be accessed exclusively from the less hindered α-face of the sodium enolate under the influence of the adjacent C5 stereocenter, leading to establishment of the requisite asymmetric quaternary carbon center at C4 in **18**.



Scheme 2 Synthesis of intermediate **5**. *Reagents and conditions*: (a) PMBCl, NaH, DMSO, r.t., 70%; (b) H_2, Raney Ni, EtOH, r.t., 86%; (c) $Ph_3MeP^+Br^-$, *t*-BuOK, benzene, reflux, 86%; (d) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, then *i*-Pr_2NEt, –78 to 0 °C, 95%; (e) $NaClO_2$, NaH_2PO_4, DMSO–H_2O (4:1), r.t.; (f) CH_2N_2, Et_2O, MeOH, 0 °C, 78% (2 steps).



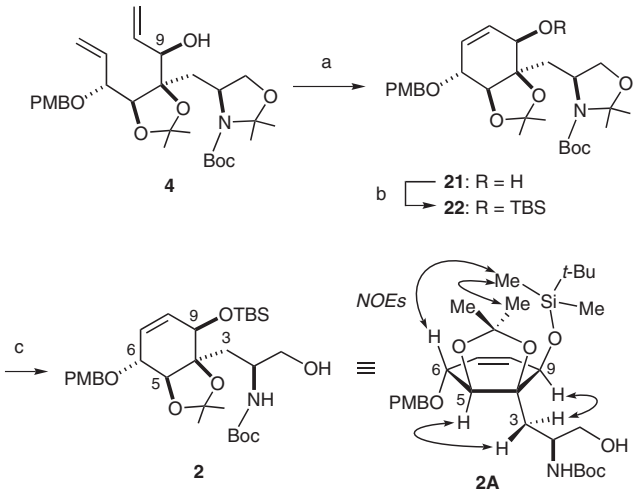
Scheme 3 Synthesis of intermediate **4**. *Reagents and conditions*: (a) NaHMDS, THF, –78 °C, then Garner aldehyde (**6**), THF, –78 °C, 69%; (b) NaHMDS, THF, 0 °C, then CS_2, then MeI, 0 °C to r.t.; (c) *n*-Bu_3SnH, AIBN, toluene, reflux, 53% (2 steps) (92% based on recovery of **18**); (d) DIBAL-H, CH_2Cl_2, –100 °C, 88%; (e) $H_2C{=}CH_2MgBr$, THF, 0 °C, 93%.

The secondary hydroxy group in **18** was eliminated by use of the Barton–McCombie protocol,[17] to give the deoxygenated product **19** in 53% overall yield (92% yield based on recovery of **18**). At this stage, the C4 stereochemistry could be unambiguously confirmed by 500-MHz ^1H NMR NOESY experiments of **19**, in which a clear NOE interaction between C3-H and C5-H was observed.

To continue the synthesis, methyl ester **19** was reduced with diisobutylaluminum hydride in dichloromethane at –100 °C, providing the corresponding aldehyde **20** in 88% yield. Subsequent Grignard reaction of **20** with vinylmagnesium bromide in tetrahydrofuran at 0 °C furnished diene **4** in 93% yield as the single diastereomer. This reaction proceeded presumably through the usual Felkin–Anh model. The C9 stereochemistry of **4** was later confirmed by a NOESY experiment of the transformed compound **2** (see below).

Synthesis of Cyclohexenone Segment 2

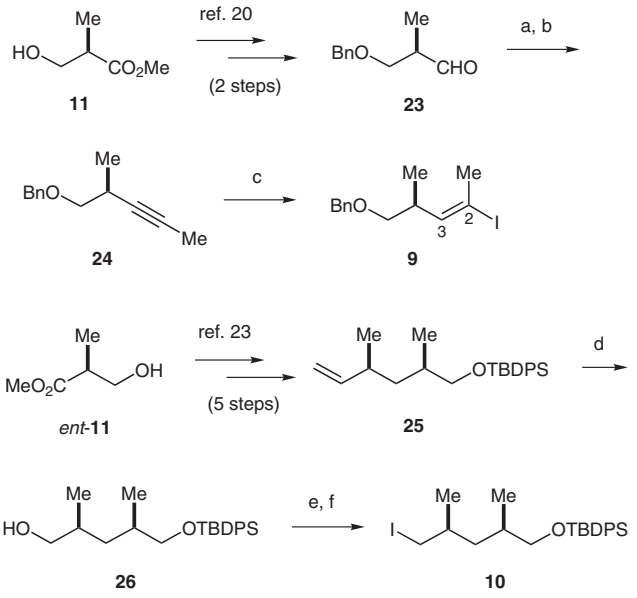
We next conducted the synthesis of the cyclohexene segment **2** as shown in Scheme 4. The critical RCM reaction[18] of diene **4** proceeded smoothly and cleanly in refluxing dichloromethane in the presence of the first-generation Grubbs catalyst $[RuCl_2(=CHPh)(PCy_3)_2]$[19] (10 mol%) for 12 hours, and the desired cyclohexene **21** was produced in 96% yield. After protection of the secondary hydroxy group in **21** (93% yield), the *N*,*O*-isopropylidene group of the resulting *tert*-butyldimethylsilyl ether **22** was selectively cleaved by treatment with pyridinium *p*-toluenesulfonate in ethanol at 60 °C; this gave the requisite cyclohexene segment **2** in 57% yield (84% yield based on recovery of **22**). At this stage, the C9 configuration of the Grignard reaction product **4** (cf. Scheme 3) was determined to be *R* by an NOESY experiment of **2**; the selected NOE correlation is depicted in the formula **2A** (Scheme 4): clear NOE interactions between a C3-H and C5-H, a C3-H and C9-H, an -OSiMe group and an isopropylidene Me group, and an -OSiMe group and C6-H are observed; this revealed an *R*-configuration at C9.



Scheme 4 Synthesis of intermediate **2**. *Reagents and conditions*: (a) $[RuCl_2(=CHPh)(PCy_3)_2]$ (10 mol%), CH_2Cl_2, reflux, 96%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, r.t., 93%; (c) PPTS, EtOH, 60 °C, 57% (84% based on recovery of **22**).

Syntheses of Vinyl Iodide 9 and Alkyl Iodide 10

Having established the synthetic pathway to the cyclohexene segment **2** possessing the requisite multifunctional groups and all the correct stereochemistries, we next undertook the syntheses of vinyl iodide **9** and alkyl iodide **10**, both key intermediates for the synthesis of the 20-carbon fatty acid segment **3**. As shown in Scheme 5, vinyl iodide **9** was prepared from the known aldehyde **23**,[20] easily derived from commercially available methyl (*R*)-3-hydroxy-2-methylpropionate (**11**). Thus, aldehyde **23** was subjected to Corey–Fuchs acetylene formation–methylation[21] to afford methylacetylene **24** in 94% yield. Subsequent hydrozirconation–iodination[22] (Cp_2ZrHCl, benzene, 40 °C; I_2, r.t.) of **24** produced the desired vinyl iodide **9** in 70% yield as a mixture of 2- and 3-iodo regioisomers (2-I/3-I, 87:17 by 500-MHz ^{1}H NMR) that were very difficult to separate.



Scheme 5 Synthesis of intermediates **9** and **10**. *Reagents and conditions*: (a) PPh_3, CBr_4, CH_2Cl_2, 0 °C; (b) *n*-BuLi, THF, –78 °C, then MeI, 0 °C, 94% (2 steps); (c) Cp_2ZrHCl, benzene, 40 °C, then I_2, r.t., 70%; (d) O_3, CH_2Cl_2–MeOH (3:1), –78 °C, then $NaBH_4$, r.t., 84%; (e) MsCl, Et_3N, CH_2Cl_2, r.t.; (f) NaI, acetone, reflux, 95% (2 steps).

Alkyl iodide **10**, the coupling partner of **9**, was prepared from the known olefin **25**[23] that was accessed from the commercially available *S*-isomer of **11** (*ent*-**11**) (Scheme 5). Thus, ozonolysis of **25** followed by reductive workup with sodium borohydride provided the corresponding alcohol **26** in 84% yield. Compound **26** was then converted into alkyl iodide **10** in 95% overall yield in a two-step sequence involving conventional mesylation and iodination.

Synthesis of the C-20 Fatty Acid Segment 3

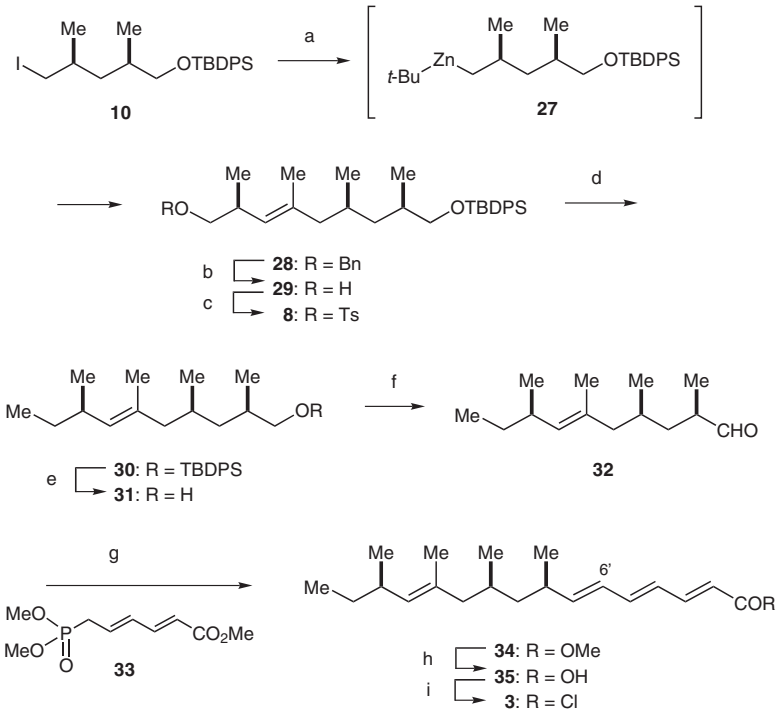
With both vinyl iodide **9** and alkyl iodide **10** in hand, our next efforts were devoted to the synthesis of the 20-carbon fatty acid segment **3**, as shown in Scheme 6. Our initial attempts to realize the crucial Negishi coupling reaction of **10** and **9** under the original conditions[24,25] [e.g., *t*-BuLi (2.0 equiv), $ZnCl_2$ (1.0 equiv), THF or Et_2O, –78 °C to r.t. for preparation of the zinc reagent of **10**; $Pd(PPh_3)_4$, THF or Et_2O, r.t. to 50 °C for the coupling reaction with **9**] resulted in failure; the coupling product **28** was not obtained. The preparation of the zinc reagent of **10** with activated zinc, Rieke zinc, and a zinc–copper couple was also unsuccessful. After several experiments, to our delight, we found that the use of the modified conditions developed by Smith et al.[26] gave satisfactory results. Thus, a mixture of **10** and one equivalent of zinc(II) chloride in diethyl ether was treated with three equivalents of *tert*-butyllithium to generate the putative mixed zinc reagent **27**,[26] which was allowed to react with vinyl iodide **9** in the presence of tetrakis(triphenylphosphine)palladium (10 mol%) in tetrahydrofuran at room temperature for 13 hours, leading to the desired coupling product **28** in 84% yield. In this reaction, the minor inseparable 3-iodo regioisomer of **9**, as we expected, did not give the corresponding coupling product and was recovered unchanged.

In the next stage, we examined the conversion of the coupling product **28** into the Hoye intermediate **8** (Scheme 6). Initial attempts to remove the benzyl protecting group from **28** under Birch conditions [Li (20 equiv), NH_3(l), tetrahydrofuran, –30 °C] turned out to be fruitless; unexpectedly, the benzene rings of the *tert*-butyldiphenylsilyl group were predominantly reduced to form the corresponding cyclohexa-1,4-diene rings. After several trials, we were pleased to find that lithium 4,4′-di-*tert*-butylbiphenylide (LiDBB)[27] was quite effective for this purpose; the desired alcohol **29** was obtained in 90% yield. Subsequent tosylation of **29** under standard conditions delivered the Hoye intermediate **8**.[10]

Further transformation of tosylate **8** into aldehyde **32** (Scheme 6) proceeded via intermediates **30** and **31** by sequential methylation with Me_2CuLi (97% yield), deprotection of the *tert*-butyldiphenylsilyl group in **30** with tetrabutylammonium fluoride (91% yield), and oxidation of **31** with *n*-Pr_4NRuO_4.[28] Aldehyde **32** was then subjected to the HWE reaction with the known dimethyl phosphonate **33**[29] to provide methyl ester **34** (46% yield from **31**) and its 6′*Z*-isomer (17% yield from **31**); these products were separated by HPLC. Spectral data (^{1}H NMR and ^{13}C NMR, MS) of **34** were in good agreement with those reported by Kogen et al.[9] Finally, the desired acid chloride **3** was synthesized from **34** via carboxylic acid **35** by alkali hydrolysis of **34** with two molar potassium hydroxide followed by reaction with oxalyl chloride in the presence of *N*,*N*-dimethylformamide.

Completion of the Total Synthesis of (+)-Scyphostatin (1)

The final route that led to completion of the total synthesis of (+)-scyphostatin (**1**) is summarized in Scheme 7. At first, we investigated the coupling reaction between the cyclohexene segment **2** and the fatty acid segment **3**.

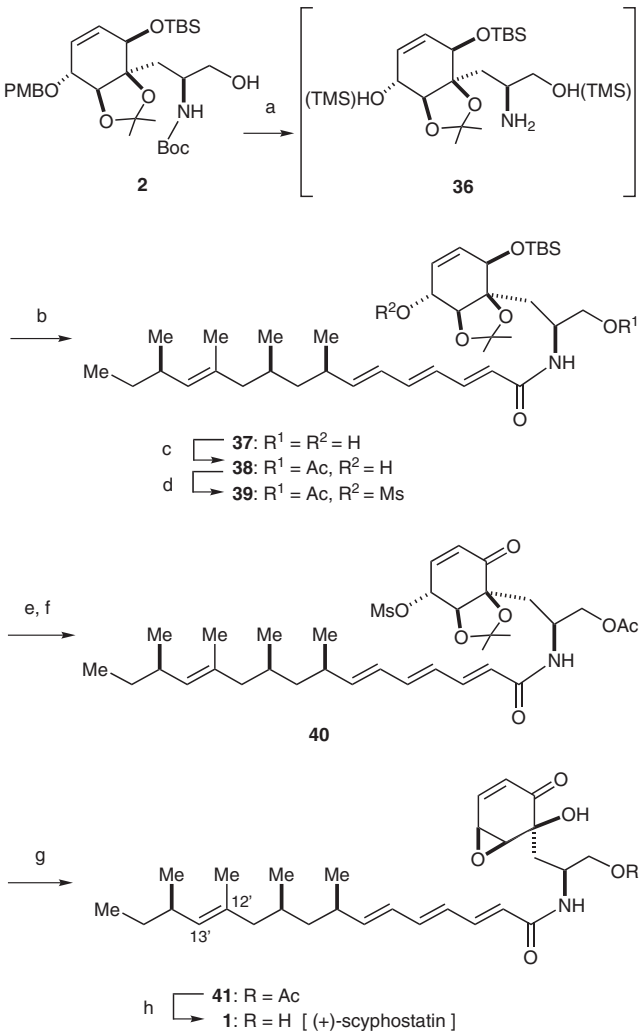


Scheme 6 Synthesis of the intermediate **3**. *Reagents and conditions*: (a) *t*-BuLi, $ZnCl_2$, Et_2O, –78 to 0 °C, then **9**, $Pd(PPh_3)_4$, THF, r.t., 81%; (b) LiDBB, THF, –78 °C, 90%; (c) TsCl, Et_3N, DMAP, CH_2Cl_2, r.t.; (d) Me_2CuLi, Et_2O, –40 °C, 97% (2 steps); (e) TBAF, THF, r.t., 91%; (f) *n*-Pr_4NRuO_4, NMO, MS, CH_2Cl_2, r.t.; (g) **33**, LDA, THF, –78 to –30 °C, 46% (2 steps); (h) 2 M aq KOH, MeOH–THF, r.t.; (i) $(COCl)_2$, CH_2Cl_2, DMF, r.t.

Thus, the *tert*-butoxycarbonyl and *p*-methoxybenzyl protecting groups of **2** were simultaneously removed by treatment with trimethylsilyl triflate[30] in the presence of 2,6-lutidine to produce amine **36**, wherein the two hydroxy groups were partially protected as the trimethylsilyl ethers. The liberated amine **36** was immediately treated with acid chloride **3** in the presence of triethylamine to give the amide coupling product **37** (73% yield from **2**) upon treatment with aqueous acetic acid. Amide **37** was further converted into mesylate **39** in 67% overall yield by selective acetylation of the primary hydroxy group and subsequent mesylation of the secondary hydroxy group in the resulting acetate **38**. Deprotection of the *tert*-butyldimethylsilyl group in **39** followed by Dess–Martin oxidation[31] furnished enone **40** in 98% yield for the two steps.

The remaining task to complete the projected synthesis was cleavage of the *N*,*O*-isopropylidene moiety in **40** followed by epoxide-ring formation and final deprotection of the acetyl group. In our preliminary model studies,[12] the epoxide-ring formation was successfully achieved by hydrolysis of an *N*,*O*-isopropylidene moiety with aqueous trifluoroacetic acid followed by treatment with one molar sodium hydroxide at 0 °C. Upon applying these conditions to **40**, however, partial isomerization of the C12′–C13′ double bond in the side chain was observed; this is presumably due to the use of a strong acid such as trifluoroacetic acid. Less strong acids such as *p*-toluenesulfonic acid, pyridinium *p*-toluenesulfonate, hydrogen chloride, boron trifluoride–diethyl ether complex, iron(III) chloride–silica gel, and acetic acid turned out to be ineffective; the corresponding diol was not obtained and the starting material **40** was recovered unchanged. Eventually, we overcame this problem by using aqueous trichloroacetic acid; this, followed by treatment with two molar sodium hydroxide at ambient temperature, produced the desired epoxide **41** in 45% overall yield (82% yield based on recovery of **40**) without appreciable isomerization of the C12′–C13′ double bond (Scheme 7).

The final step was deprotection of the acetyl group in **41**. Initial attempts to achieve this under conventional conditions (e.g., K_2CO_3, NaOMe, KOH in MeOH, aq KOH in THF or CH_2Cl_2, DBU or NH_3 in THF) resulted in failure; disappearance of the starting material **41** could be ascertained by TLC analysis, while unidentified decomposition products were generated in the reaction mixture. We reasoned that this failure was due to the sensitivity of the epoxyenone moiety to these basic conditions. Therefore, we decided to attempt the acetyl deprotection by an enzymatic method in the hope that the sensitive epoxyenone system would remain intact under such relatively mild conditions. After the screening of several enzymes such as lipases PS, AY-30G, and F-AP15, we were pleased to find that the desired acetyl deprotection was best achieved by the use of lipase PS. Thus, exposure of **41** to lipase PS in phosphate buffer–acetone at room temperature for ten hours provided (+)-scyphostatin (**1**) in 60% yield (Scheme 7); the spectroscopic properties (IR, ^{1}H NMR and ^{13}C NMR, and MS) of this product were identical with those of natural **1**. The optical rotation of a synthetic sam-



Scheme 7 Synthesis of (+)-scyphostatin (**1**). *Reagents and conditions*: (a) TMSOTf, 2,6-lutidine, CH_2Cl_2, r.t., then MeOH; (b) **3**, Et_3N, CH_2Cl_2, r.t., then aq AcOH, 73% (2 steps); (c) Ac_2O, py, DMAP, CH_2Cl_2, r.t., 72%; (d) MsCl, Et_3N, CH_2Cl_2, r.t., 93%; (e) TBAF, THF, r.t.; (f) DMP, CH_2Cl_2, r.t., 98% (2 steps); (g) Cl_3CCO_2H, H_2O, CH_2Cl_2, reflux, then 2 M NaOH, r.t., 45% (82% based on recovery of **40**); (h) lipase PS, pH 7 phosphate buffer, acetone, r.t., 60%.

ple of **1** {$[\alpha]_D^{25}$ +61.0 (*c* 0.04, MeOH)} was identical to that of natural **1** {$[\alpha]_D^{25}$ +66.4 (*c* 0.09, MeOH)}.

Conclusion

We have accomplished the first total, enantioselective synthesis of naturally occurring (+)-scyphostatin (**1**), starting from D-arabinose derivative **12** in 22 steps (linear sequence of reactions). The key steps of the synthesis were (a) a stereoselective aldol-type coupling reaction of ester **5**, derived from D-arabinose (**7**), with Garner aldehyde (**6**) to establish the requisite asymmetric quaternary carbon center at C4; (b) RCM reaction of diene **4** to construct the cyclohexene ring **21**; (c) Negishi coupling between alkyl iodide **10** and vinyl iodide **9** to give trisubstituted *E*-olefin **28**; (d) amide formation to connect the cyclohexene segment **2** and the fatty acid segment **3**; and (e) stereospecific epoxide-ring formation of mesylate **40** to deliver the fully functionalized cyclohexene **2**. Importantly, the explored synthetic route has the potential for producing scyphostatin analogues possessing a variety of fatty acid side chains in enantiomerically pure forms. These efforts are currently underway.

Routine monitoring of reactions was carried out on glass-supported Merck silica gel 60 F_{254} TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60N (spherical, neutral 40–50 μm) with the solvents indicated at the pertinent procedures. All solvents and reagents were used as supplied, with the following exceptions. THF and Et_2O were freshly distilled from Na/benzophenone under argon. Toluene was distilled from Na under argon. CH_2Cl_2, DMSO, DMF, and benzene were distilled from CaH_2 under argon. Optical rotations were measured on a JASCO P-1020 automatic digital polarimeter. Melting points were determined on a Yanaco MP-3 micro melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker DRX-500 (500 MHz) spectrometer. Chemical shifts are expressed in ppm relative to TMS (δ = 0) as internal standard. IR spectra were measured on a JASCO FT/IR-5300 spectrometer. HRMS spectra were obtained on a JEOL MStation JMS-700 mass spectrometer.

Benzyl 3,4-*O*-Isopropylidene-2-*O*-(4-methoxybenzyl)-β-D-arabinoside (13)

A soln of **12**[16] (5.00 g, 18 mmol) in anhyd DMSO (10 mL) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil; 1.00 g, 25 mmol) in anhyd DMSO (15 mL) at 0 °C under argon. After the mixture had stirred for 1 h at r.t., PMBCl (3.10 mL, 23 mmol) was added, and stirring was continued for 15 h at r.t. The reaction was quenched with sat. aq NH_4Cl (10 mL) at 0 °C, and the resulting mixture was extracted with Et_2O (2 × 50 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (2 × 30 mL) and brine (30 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 3:1) to give a white solid; yield: 5.00 g (70%).

White powder (recrystallization, hexane–$CHCl_3$, 3:1); mp 52.0–53.0 °C; $[\alpha]_D^{20}$ –160.6 (*c* 1.04, $CHCl_3$).

IR (KBr): 744, 1030, 1091, 1178, 1255, 1383, 1516, 1612, 2926, 2951, 3024 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 1.43 (s, 3 H), 3.52 (dd, *J* = 3.4, 7.8 Hz, 1 H), 3.79 (s, 3 H), 3.92 (dd, *J* = 0.7, 3.3 Hz, 1 H), 3.97 (dd, *J* = 2.7, 3.3 Hz, 1 H), 4.22 (m, 1 H), 4.36 (dd, *J* = 5.7, 7.8 Hz, 1 H), 4.52 (d, *J* = 12.4 Hz, 1 H), 4.56 (d, *J* = 12.1 Hz, 1 H), 4.65 (d, *J* = 12.1 Hz, 1 H), 4.72 (d, *J* = 12.4 Hz, 1 H), 4.81 (d, *J* = 3.4 Hz, 1 H), 6.83 (d, *J* = 8.7 Hz, 2 H), 7.23 (d, *J* = 8.7 Hz, 2 H), 7.28–7.40 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.3, 28.2, 55.3, 58.9, 69.2, 71.8, 73.5, 75.4, 76.4, 95.8, 108.8, 113.7 (2 C), 127.8, 127.9 (2 C), 128.4 (2 C), 129.4 (2 C), 130.4, 137.3, 159.2.

Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found C, 68.87; H, 7.18.

3,4-*O*-Isopropylidene-2-*O*-(4-methoxybenzyl)-D-arabinose (14)

A mixture of **13** (5.00 g, 12.5 mmol) and Raney Ni (W-2, 5.00 g) in EtOH (50 mL) was stirred for 12 h under H_2 (1 atm) at r.t. The mixture was diluted with EtOAc (50 mL), and then the catalyst was removed by filtration of the mixture through a small pad of Celite. Concentration of the filtrate in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 2:1 to 1:1);

this gave a mixture of α- and β-anomers **14** (α/β, 1:2) as a white semisolid.

Yield: 2.50 g (86%); $[\alpha]_D^{20}$ –47.0 (*c* 1.00, $CHCl_3$).

Recrystallization of the anomeric mixtures (hexane–$CHCl_3$, 3:1) gave pure β-anomer **14** as white needles.

Mp 115.5–116.5 °C; $[\alpha]_D^{20}$ –49.4 (*c* 1.00, $CHCl_3$).

IR (KBr): 778, 1035, 1066, 1177, 1244, 1377, 1510, 1612, 2932, 2959, 3013, 3323 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (α-anomer) = 1.36 (s, 3 H), 1.48 (s, 3 H), 3.45 (d, *J* = 6.7 Hz, 1 H), 3.47 (m, 1 H), 3.80 (s, 3 H), 3.80 (ddd, *J* = 0.8, 3.4, 13.1 Hz, 1 H), 4.06 (dd, *J* = 2.1, 13.0 Hz, 1 H), 4.20–4.24 (m, 2 H), 4.69 (d, *J* = 11.4 Hz, 1 H), 4.71 (m, 1 H), 4.72 (d, *J* = 11.4 Hz, 1 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 7.31 (dd, *J* = 8.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (α-anomer) = 25.8, 27.6, 55.3, 62.5, 72.70, 72.71, 77.2, 78.8, 95.5, 109.9, 113.8 (2 C), 129.7 (2 C), 130.0, 159.4.

^1H NMR (500 MHz, $CDCl_3$): δ (β-anomer) = 1.36 (s, 3 H), 1.46 (s, 3 H), 3.09 (d, *J* = 5.7 Hz, 1 H), 3.60 (dd, *J* = 3.4, 5.9 Hz, 1 H), 3.80 (s, 3 H), 3.83 (dd, *J* = 2.0, 13.0 Hz, 1 H), 4.12 (dd, *J* = 3.0, 13.0 Hz, 1 H), 4.23 (m, 1 H), 4.37 (t, *J* = 6.0 Hz, 1 H), 4.61 (d, *J* = 11.7 Hz, 1 H), 4.74 (d, *J* = 11.7 Hz, 1 H), 5.11 (dd, *J* = 3.4, 5.7 Hz, 1 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 7.27 (dd, *J* = 8.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (β-anomer) = 25.9, 27.7, 55.3, 60.0, 72.4, 72.6, 74.4, 75.6, 90.9, 109.2, 113.9 (2 C), 129.71 (2 C), 129.73, 159.5.

HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{23}O_6$: 311.1495; found: 311.1509.

(2*R*,3*S*,4*R*)-2,3-*O*-Isopropylidene-4-(4-methoxybenzyloxy)hex-5-ene-1,2,3-triol (15)

t-BuOK (3.10 g, 28 mmol) was added to a stirred suspension of $Ph_3MeP^+Br^-$ (10.4 g, 29 mmol) in anhyd benzene (80 mL), and the resulting mixture was heated at reflux for 3 h under argon. A soln of **14** (1.75 g, 5.6 mmol) in anhyd THF (40 mL) was added to the phosphorane soln, and the resulting mixture was heated at reflux for 1 h. After cooling, the reaction mixture was quenched with sat. aq NH_4Cl (40 mL) at 0 °C, and then extracted with Et_2O (2 × 60 mL). The organic layer was washed successively with sat. aq $NaHCO_3$ (2 × 40 mL) and brine (40 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 4:1).

Yield: 1.50 g (86%); colorless oil; $[\alpha]_D^{20}$ –19.4 (*c* 1.04, $CHCl_3$).

IR (neat): 756, 933, 1037, 1248, 1379, 1514, 1612, 2839, 2986, 3076, 3474 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.50 (s, 3 H), 2.60 (dd, *J* = 5.3, 7.9 Hz, 1 H), 3.66 (dt, *J* = 11.8, 5.6 Hz, 1 H), 3.72 (ddd, *J* = 4.9, 7.9, 11.8 Hz, 1 H), 3.80 (s, 3 H), 3.96 (dd, *J* = 5.3, 7.9 Hz, 1 H), 4.18 (dt, *J* = 5.1, 6.0 Hz, 1 H), 4.24 (dd, *J* = 5.4, 6.2 Hz, 1 H), 4.38 (d, *J* = 11.5 Hz, 1 H), 4.61 (d, *J* = 11.5 Hz, 1 H), 5.36 (d, *J* = 17.3 Hz, 1 H), 5.40 (d, *J* = 10.3 Hz, 1 H), 5.91 (ddd, *J* = 8.0, 10.3, 17.3 Hz, 1 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 7.26 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.4, 27.2, 55.2, 61.2, 70.1, 77.7, 78.0, 78.8, 108.7, 113.8 (2 C), 120.3, 129.5, 129.6 (2 C), 134.8, 159.3.

HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{25}O_5$: 309.1702; found: 309.1700.

(2*S*,3*S*,4*R*)-2,3-*O*-Isopropylidenedioxy-4-(4-methoxybenzyloxy)hex-5-enal (16)

DMSO (2.52 mL, 36 mmol) was added dropwise to a stirred soln of oxalyl chloride (2.33 mL, 27 mmol) in CH_2Cl_2 (80 mL) at –78 °C under argon. After 20 min, a soln of **15** (2.74 g, 8.9 mmol) in CH_2Cl_2 (40 mL) was added at –78 °C, and stirring was continued for 30 min at the same temperature. After addition of *i*-Pr_2NEt (12.0 mL, 69 mmol) at –78 °C, the mixture was gradually warmed to 0 °C over 1 h. The reaction was quenched with H_2O (20 mL) at 0 °C, and the mixture was extracted with Et_2O (2 × 80 mL). The combined extracts were washed successively with 3% aq HCl (2 × 50 mL), sat. aq $NaHCO_3$ (2 × 40 mL), and brine (50 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 5:1).

Yield: 2.59 g (95%); colorless oil; $[\alpha]_D^{20}$ –75.2 (*c* 1.00, $CHCl_3$).

IR (neat): 831, 1033, 1072, 1250, 1381, 1516, 1614, 1724, 2868, 2988, 3076 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.57 (s, 3 H), 3.78 (dd, *J* = 2.4, 8.2 Hz, 1 H), 3.80 (s, 3 H), 4.01 (d, *J* = 10.9 Hz, 1 H), 4.37 (dd, *J* = 2.0, 8.2 Hz, 1 H), 4.39 (d, *J* = 10.9 Hz, 1 H), 4.49 (dd, *J* = 2.4, 8.1 Hz, 1 H), 5.35 (d, *J* = 17.3 Hz, 1 H), 5.38 (d, *J* = 10.3 Hz, 1 H), 5.94 (ddd, *J* = 8.1, 10.3, 17.3 Hz, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 7.22 (d, *J* = 8.7 Hz, 2 H), 9.56 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.1, 26.5, 55.2, 69.5, 77.6, 80.5, 82.9, 111.2, 113.6 (2 C), 119.9, 129.2 (2 C), 129.9, 134.3, 159.1, 201.3.

HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{23}O_5$: 307.1546; found: 307.1559.

Methyl (2*S*,3*S*,4*R*)-2,3-*O*-Isopropylidenedioxy-4-(4-methoxybenzyloxy)hex-5-enoate (5)

$NaClO_2$ (4.52 g, 50 mmol) was added in small portions to a stirred soln of **16** (3.04 g, 9.9 mmol) and NaH_2PO_4 (7.76 g, 50 mmol) in DMSO–H_2O (4:1, 100 mL) at r.t. After 1 h, the reaction was quenched with 15% aq $Na_2S_2O_3$ (30 mL) at 0 °C, and the mixture was extracted with EtOAc (3 × 70 mL). The organic layer was washed with brine (2 × 50 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded the corresponding carboxylic acid (2.80 g), which was directly, without further purification, used for the next reaction.

A 0.5 M soln of CH_2N_2 in Et_2O (24.0 mL, 12 mmol) was added dropwise to a stirred soln of the crude carboxylic acid (2.80 g) in MeOH (20 mL) at 0 °C, and stirring was continued for 30 min at r.t. The reaction was quenched with AcOH (2.0 mL) at 0 °C, and the resulting mixture was diluted with Et_2O (100 mL). The organic layer was washed with sat. aq $NaHCO_3$ (3 × 30 mL) and brine (30 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 3:1); this gave **5** as a colorless oil.

Yield: 2.61 g (78%, over 2 steps); $[\alpha]_D^{20}$ –34.2 (*c* 1.01, $CHCl_3$).

IR (neat): 823, 1076, 1248, 1381, 1514, 1614, 1730, 1761, 2839, 2988, 3076 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.60 (s, 3 H), 3.53 (s, 3 H), 3.79 (s, 3 H), 4.01 (dd, *J* = 4.0, 8.0 Hz, 1 H), 4.20 (d, *J* = 11.5 Hz, 1 H), 4.43 (dd, *J* = 4.0, 7.3 Hz, 1 H), 4.51 (d, *J* = 11.5 Hz, 1 H), 4.67 (d, *J* = 7.3 Hz, 1 H), 5.34 (d, *J* = 17.3 Hz, 1 H), 5.36 (d, *J* = 10.4 Hz, 1 H), 5.90 (ddd, *J* = 8.0, 10.4, 17.3 Hz, 1 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 7.23 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.5, 26.6, 51.8, 55.2, 69.7, 75.3, 78.4, 80.4, 110.8, 113.5 (2 C), 119.7, 128.5 (2 C), 130.4, 134.8, 158.8, 170.2.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{25}O_6$: 337.1651; found: 337.1668.

Methyl (2*S*,3*S*,4*R*)-2-{[(4*R*)-3-*tert*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl]hydroxymethyl}-2,3-*O*-isopropylidenedioxy-4-(4-methoxybenzyloxy)hex-5-enoate (18)

A 1.0 M soln of NaHMDS in THF (2.96 mL, 3.0 mmol) was added dropwise to a stirred soln of **5** (796 mg, 2.4 mmol) in anhyd THF (25 mL) at 0 °C under argon. After 20 min, a soln of the Garner aldehyde (**6**; 598 mg, 2.6 mmol) in anhyd THF (10 mL) was added at –78 °C, and the resulting soln was stirred for 4 h at the same temperature. The reaction was quenched with sat. aq NH_4Cl (20 mL) at –78 °C, and the mixture was extracted with Et_2O (2 × 50 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (2 × 30 mL) and brine (30 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 8:1 to 5:1); this gave **18** as a white solid; yield: 930 mg (69%). (Note that the presence of rotamers in the *tert*-butyl carbamate group resulted in extensive line broadening, and, in some instances, doubling of signals in the ^{1}H NMR and ^{13}C NMR spectra.)

Colorless needles (recrystallization, hexane–CH_2Cl_2, 4:1); mp 86.5–88.0 °C; $[\alpha]_D^{20}$ –13.1 (*c* 1.08, $CHCl_3$).

IR (KBr): 772, 843, 1067, 1251, 1370, 1399, 1518, 1614, 1688, 1724, 2939, 2982, 3090, 3489 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46 (br s, 3 H), 1.49 (br s, 3 H), 1.50 (br s, 9 H), 1.62 (s, 6 H), 2.52 (br s, 0.5 H), 2.93 (br s, 0.5 H), 3.46 (s, 3 H), 3.78 (s, 3 H), 3.85 (dd, *J* = 6.5, 9.6 Hz, 1 H), 3.90–4.10 (m, 2 H), 4.14 (d, *J* = 11.4 Hz, 1 H), 4.23–4.38 (m, 2 H), 4.50 (d, *J* = 11.4 Hz, 1 H), 4.59 (br s, 1 H), 5.31–5.40 (m, 2 H), 5.96 (ddd, *J* = 8.0, 10.3, 17.6 Hz, 1 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 7.21 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.0 (4 C), 28.5 (3 C), 52.0, 55.2, 58.9, 63.7, 69.7, 71.8, 77.3, 80.5, 83.7, 86.2, 93.5, 111.7, 113.5 (2 C), 119.2, 128.4 (2 C), 130.6, 135.5, 152.3, 158.8, 171.3.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{44}NO_{10}$: 566.2965; found: 566.2938.

Methyl (2*S*,3*S*,4*R*)-2-{[(4*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl]methyl}-2,3-*O*-isopropylidenedioxy-4-(4-methoxybenzyloxy)hex-5-enoate (19)

A 1.0 M soln of NaHMDS in THF (4.00 mL, 4.0 mmol) was added dropwise to a stirred soln of **18** (924 mg, 1.6 mmol) in anhyd THF (35 mL) at 0 °C under argon. After 20 min, CS_2 (0.90 mL, 15 mmol) was added dropwise to the above soln at 0 °C, and stirring was continued for 20 min at the same temperature. MeI (1.00 mL, 16 mmol) was then added dropwise to the stirred soln at 0 °C, and then the resulting soln was allowed to warm to r.t. over 30 min. The reaction was quenched with sat. aq NH_4Cl (10 mL) at 0 °C, and the mixture was extracted with Et_2O (3 × 40 mL). The organic layer was washed with sat. aq $NaHCO_3$ (2 × 30 mL) and brine (30 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was immediately passed through silica gel (hexane–EtOAc, 2:1); this gave the corresponding methyl xanthate (1.35 g) as a colorless oil, which was directly used for the next reaction without further purification.

n-Bu_3SnH (1.20 mL, 4.5 mmol) and AIBN (66.0 mg, 0.40 mmol) were added successively to a soln of the crude methyl xanthate (1.35 g) in toluene (40 mL). For the deaeration of the reaction mixture, it was frozen in liquid N_2, and the reaction vessel was evacuated in vacuo for 30 min before being filled with dry argon. The mixture was heated at reflux for 1 h under argon. After cooling, the reaction mixture was concentrated in vacuo; this afforded a residue, which was purified by column chromatography (hexane–EtOAc, 10:1 to 3:1); this gave **19** as a colorless oil. (Note that the presence of rotamers in the *tert*-butyl carbamate group resulted in extensive line broadening, and, in some instances, doubling of signals in the ^{1}H NMR and ^{13}C NMR spectra.)

Yield: 475 mg [53%, or 92% based on recovery of starting material **18** (389 mg, 42%)]; $[\alpha]_D^{20}$ –10.4 (*c* 0.72, $CHCl_3$).

IR (neat): 770, 852, 1088, 1249, 1389, 1516, 1615, 1698, 1732, 2937, 2982, 3080 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.45 (s, 6 H), 1.47 (s, 9 H), 1.56 (br s, 3 H), 1.59 (s, 3 H), 1.82 (br s, 1 H), 2.45 (br s, 0.5 H), 2.65 (br s, 0.5 H), 3.51 (s, 3 H), 3.78 (s, 3 H), 3.79 (br, 1 H), 3.85 (br, 1 H), 4.03 (d, *J* = 2.8 Hz, 1 H), 4.08 (br, 1 H), 4.19 (d, *J* = 11.4 Hz, 1 H), 4.25 (br, 1 H), 4.48 (br, 1 H), 5.31–5.41 (m, 2 H), 5.95 (ddd, *J* = 7.8, 10.3, 17.7 Hz, 1 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 7.22 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.0 (2 C), 27.7 (3 C), 28.5 (2 C), 41.4, 52.0, 54.8, 55.2, 67.1, 69.8, 78.0, 79.9, 84.0, 87.8, 93.1, 111.4, 113.5 (2 C), 119.4, 128.4 (2 C), 130.5, 134.9, 151.6, 158.8, 171.6.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{44}NO_9$: 550.3016; found: 550.3039.

(2*S*,3*S*,4*R*)-2-{[(4*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl]methyl}-2,3-*O*-isopropylidenedioxy-4-(4-methoxybenzyloxy)hex-5-enal (20)

A 1.0 M soln of DIBAL-H in toluene (0.11 mL, 0.11 mmol) was added dropwise to a stirred soln of **19** (54.0 mg, 0.10 mmol) in anhyd CH_2Cl_2 (2 mL) at –100 °C under argon. After 1 h, the reaction was quenched with MeOH (1 mL) at –100 °C. A 15% aq soln of Rochelle salt (5 mL) was added to the mixture at 0 °C, and stirring was continued for 1 h at r.t. The resulting mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine (2 × 20 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 5:1); this gave **20** as a colorless oil. (Note that the presence of rotamers in the *tert*-butyl carbamate group resulted in extensive line broadening, and, in some instances, doubling of signals in the ^{1}H NMR and ^{13}C NMR spectra.)

Yield: 45.0 mg (88%); $[\alpha]_D^{20}$ –30.5 (*c* 0.63, $CHCl_3$).

IR (neat): 770, 849, 1092, 1250, 1389, 1516, 1614, 1698, 1730, 2935, 2982, 3070 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.47 (s, 6 H), 1.49 (s, 9 H), 1.55 (s, 3 H), 1.57 (br s, 3 H), 1.75 (br, 1 H), 2.41 (br s, 0.5 H), 2.65 (br s, 0.5 H), 3.75 (br, 1 H), 3.79 (s, 3 H), 3.82–3.90 (br, 2 H), 4.02 (d, *J* = 2.9 Hz, 1 H), 4.05–4.20 (br, 2 H), 4.44 (br, 1 H), 5.33–5.43 (m, 2 H), 5.91 (ddd, *J* = 8.0, 10.3, 17.3 Hz, 1 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 7.22 (d, *J* = 8.6 Hz, 2 H), 9.52 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.6 (4 C), 28.5 (3 C), 39.2, 54.3, 55.2, 67.7, 69.9, 77.2, 80.1, 87.3, 89.0, 93.3, 111.7, 113.7 (2 C), 119.9, 129.6 (3 C), 134.4, 151.7 159.2, 200.6.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{42}NO_8$: 520.2910; found: 520.2883.

(3*R*,4*R*,5*S*,6*R*)-4-{[(4*S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl]methyl}-4,5-*O*-isopropylidene-6-(4-methoxybenzyloxy)octa-1,7-diene-3,4,5-triol (4)

A 0.97 M soln of $H_2C{=}CH_2MgBr$ in THF (0.50 mL, 0.49 mmol) was added dropwise to a stirred soln of **20** (58.0 mg, 0.11 mmol) in anhyd THF (2.5 mL) at 0 °C under argon. After 1 h, the reaction was quenched with sat. aq NH_4Cl (5 mL) at 0 °C, and the mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (2 × 20 mL) and brine (20 mL), and dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 6:1); this gave **4** as a colorless oil. (Note that the presence

of rotamers in the *tert*-butyl carbamate group resulted in extensive line broadening, and, in some instances, doubling of signals in the ^{1}H NMR and ^{13}C NMR spectra.)

Yield: 57 mg (93%); $[\alpha]_D^{20}$ +17.5 (*c* 1.21, $CHCl_3$).

IR (neat): 770, 855, 1107, 1248, 1393, 1514, 1615, 1670, 1700, 2935, 2982, 3090, 3423 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 6 H), 1.40 (s, 3 H), 1.46 (s, 9 H), 1.51 (s, 3 H), 1.58 (m, 0.7 H), 1.73 (br, 0.3 H), 2.18 (br, 0.3 H), 2.29 (br d, 0.7 H, *J* = 14.5 Hz), 3.10 (br, 0.3 H), 3.73 (d, *J* = 6.0 Hz, 1 H), 3.79 (s, 3 H), 3.80–4.00 (m, 1.7 H), 4.00–4.20 (br, 1 H), 4.25–4.38 (br, 2 H), 4.44 (br, 1 H), 4.47 (br d, *J* = 11.4 Hz, 1 H), 4.60 (br d, *J* = 11.4 Hz, 1 H), 5.21 (dt, *J* = 10.8, 2.0 Hz, 1 H), 5.29–5.51 (m, 3 H), 5.98 (m, 0.7 H), 6.15 (m, 0.6 H), 6.38 (m, 0.7 H), 6.85 (d, *J* = 7.7 Hz, 2 H), 7.28 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.3, 26.6, 27.6, 28.0, 28.3 (3 C), 39.7, 53.8, 55.2, 68.7, 70.2, 72.0, 80.5, 84.1, 84.5, 87.1, 92.7, 107.9, 113.7 (2 C), 114.7, 119.2, 129.4 (2 C), 130.5, 135.6, 139.0, 152.4, 159.1.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{46}NO_8$: 548.3223; found: 548.3203.

(1*S*,2*R*,3*R*,6*R*)-2-{[(4*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl]methyl}-1,2-*O*-isopropylidene-6-(4-methoxybenzyloxy)cyclohex-4-ene-1,2,3-triol (21)

$[RuCl_2(=CHPh)(PCy_3)_2]$ (24.0 mg, 29 μmol) was added to a soln of **4** (160 mg, 0.29 mmol) in anhyd CH_2Cl_2 (200 mL). For the deaeration of the reaction mixture, it was frozen in liquid N_2, and the reaction vessel was evacuated in vacuo for 30 min before being filled with dry argon. The mixture was then heated at reflux for 12 h. After cooling, the reaction mixture was stirred for 3 h at r.t. under air. Evaporation of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 8:1); this gave **21** as a colorless oil. (Note that the presence of rotamers in the *tert*-butyl carbamate group resulted in extensive line broadening, and, in some instances, doubling of signals in the ^{1}H NMR and ^{13}C NMR spectra.)

Yield: 146 mg (96%); $[\alpha]_D^{20}$ –48.9 (*c* 1.20, $CHCl_3$).

IR (neat): 772, 850, 1078, 1252, 1391, 1514, 1612, 1696, 2936, 2982, 3040, 3524 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (s, 3 H), 1.35 (s, 6 H), 1.44 (s, 3 H), 1.47 (s, 6 H), 1.60 (s, 3 H), 1.95 (dd, *J* = 11.3, 13.5 Hz, 1 H), 2.08 (dd, *J* = 10.6, 11.9 Hz, 1 H), 2.83 (d, *J* = 9.9 Hz, 1 H), 3.79 (s, 3 H), 3.91 (dd, *J* = 6.1, 8.3 Hz, 1 H), 4.02–4.30 (m, 4 H), 4.35 (m, 1 H), 4.43 (d, *J* = 11.3 Hz, 1 H), 4.52 (d, *J* = 11.3 Hz, 1 H), 5.96 (ddd, *J* = 1.8, 5.1, 9.9 Hz, 1 H), 6.04 (br d, *J* = 9.9 Hz, 1 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 7.22 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.2, 26.9, 27.0, 27.3, 28.3 (3 C), 45.3, 54.0, 55.3, 67.8, 67.9, 70.6, 70.7, 79.6, 81.6, 82.4, 93.1, 109.4, 113.8 (2 C), 126.1, 129.5 (2 C), 130.3, 137.2, 151.5, 159.4.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{42}NO_8$: 520.2910; found: 520.2887.

(1*S*,2*S*,3*R*,6*R*)-1-{[(4*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl]methyl}-6-(*tert*-butyldimethylsiloxy)-1,2-*O*-isopropylidene-3-(4-methoxybenzyloxy)cyclohex-4-ene-1,2-diol (22)

TBSOTf (0.20 μL, 0.86 mmol) was added dropwise to a stirred soln of **21** (221 mg, 0.43 mmol) in anhyd CH_2Cl_2 (12 mL) containing 2,6-lutidine (0.14 μL, 1.2 mmol) at 0 °C under argon. After 30 min at r.t., the reaction was quenched with H_2O (5 mL) at 0 °C, and the mixture was extracted with EtOAc (2 × 30 mL). The organic layer was washed with brine (2 × 20 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 10:1); this gave **22** as a colorless oil. (Note that the presence of rotamers in the *tert*-butyl carbamate group resulted in extensive line broadening, and, in some instances, doubling of signals in the ^{1}H NMR and ^{13}C NMR spectra.)

Yield: 250 mg (93%); $[\alpha]_D^{20}$ –42.2 (*c* 0.88, $CHCl_3$).

IR (neat): 775, 835, 1094, 1250, 1391, 1514, 1615, 1692, 2932, 2982, 3045 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.04 (s, 6 H), 0.83 (s, 9 H), 1.36 (s, 3 H), 1.38 (s, 15 H), 1.45 (s, 3 H), 1.78–1.90 (br, 2 H), 3.74 (s, 3 H), 3.80–4.45 (m, 6 H), 4.49 (d, *J* = 11.4 Hz, 1 H), 4.54 (d, *J* = 11.4 Hz, 1 H), 5.93 (br, 1 H), 6.05 (ddd, *J* = 1.6, 4.7, 9.7 Hz, 1 H), 6.97 (d, *J* = 8.6 Hz, 2 H), 7.25 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = –4.4, –4.2, 17.7, 25.7 (6 C), 27.0 (2 C), 28.8 (2 C), 43.2, 53.7, 54.9, 66.9, 67.7, 69.8, 74.5, 78.9, 82.7, 83.9, 92.2, 109.0, 113.5 (2 C), 129.2 (2 C), 130.0, 130.6, 132.4, 150.7, 158.6.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{56}NO_8Si$: 634.3775; found: 634. 3781.

(1*S*,2*S*,3*R*,6*R*)-1-[(2*S*)-2-(*tert*-Butoxycarbonylamino)-3-hydroxypropyl]-6-(*tert*-butyldimethylsiloxy)-1,2-*O*-isopropylidene-3-(4-methoxybenzyloxy)cyclohex-4-ene-1,2-diol (2)

A soln of **22** (212 mg, 0.34 mmol) and PPTS (50.0 mg, 0.20 mmol) in EtOH (8 mL) was heated at 60 °C for 3 h. After cooling, the reaction mixture was diluted with Et_2O (50 mL). The organic layer was washed with 1 M NaOH (15 mL) and brine (15 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 6:1); this gave **2** as a white solid; yield: 113 mg [57%, or 84% based on recovered **22** (68 mg, 32%)].

White needles (recrystallization, hexane–$CHCl_3$, 5:1); mp 112.5–113.5 °C; $[\alpha]_D^{20}$ –61.5 (*c* 1.03, $CHCl_3$).

IR (KBr): 777, 842, 1080, 1250, 1370, 1518, 1535, 1616, 1672, 2934, 2957, 3045, 3290, 3449, 3557 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.03 (s, 3 H), 0.05 (s, 3 H), 0.84 (s, 9 H), 1.42 (s, 9 H), 1.44 (s, 3 H), 1.49 (s, 3 H), 1.68 (dd, *J* = 8.0, 14.8 Hz, 1 H), 1.87 (dd, *J* = 6.0, 14.8 Hz, 1 H), 2.87 (br, 1 H), 3.63 (m, 1 H), 3.72–3.80 (m, 2 H), 3.80 (s, 3 H), 3.96 (d, *J* = 4.3 Hz, 1 H), 4.23 (d, *J* = 5.6 Hz, 1 H), 4.48 (m, 1 H), 4.57 (d, *J* = 11.3 Hz, 1 H), 4.67 (d, *J* = 11.3 Hz, 1 H), 4.82 (br, 1 H), 5.92 (dd, *J* = 2.2, 9.7 Hz, 1 H), 6.08 (m, 1 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 7.29 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.6, –4.1, 18.1, 26.0 (3 C), 27.2, 27.3, 28.4 (3 C), 42.1, 49.3, 55.3, 65.6, 67.3, 71.2, 77.3, 79.6, 83.5, 85.7, 110.3, 113.8 (2 C), 129.6 (2 C), 130.3, 131.3, 132.8, 155.5, 159.2.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{52}NO_8Si$: 594.3462; found: 594.3435.

(4*S*)-5-(Benzyloxy)-4-methylpent-2-yne (24)

CBr_4 (1.92 g, 5.8 mmol) was added to a stirred soln of (*R*)-**23**^{20} (344 mg, 1.9 mmol) and PPh_3 (3.04 g, 12 mmol) in anhyd CH_2Cl_2 (40 mL) at 0 °C. After 10 min, the mixture was quenched with sat. aq $NaHCO_3$ (15 mL), and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with brine (2 × 30 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 1:0 to 10:1); this gave the corresponding dibromoalkene (645 mg) as a colorless oil. A 1.58 M soln of *n*-BuLi in hexane (2.46 mL, 3.9 mmol) was added dropwise to a stirred soln of the dibromoalkene (645 mg, 1.9 mmol) in anhyd THF (20 mL) at –78 °C under argon. After 1 h, the reaction mixture was allowed to warm to

0 °C, and MeI (0.14 mL, 2.3 mmol) was added. The resulting soln was further stirred for 1 h at 0 °C. The reaction was quenched with sat. aq NH_4Cl (10 mL) at 0 °C, and the mixture was extracted with Et_2O (2 × 40 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (2 × 20 mL) and brine (20 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 50:1).

Yield: 342 mg (94%, 2 steps); colorless oil; $[\alpha]_D^{20}$ –3.0 (*c* 1.59, $CHCl_3$).

IR (neat): 610, 698, 735, 1028, 1097, 1204, 1360, 1454, 1497, 1605, 2859, 2971, 3030 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 6.9 Hz, 3 H), 1.80 (d, *J* = 2.4 Hz, 3 H), 2.70 (m, 1 H), 3.32 (dd, *J* = 7.5, 9.0 Hz, 1 H), 3.48 (dd, *J* = 6.1, 9.0 Hz, 1 H), 4.56 (dd, *J* = 12.2, 16.2 Hz, 2 H), 7.27–7.37 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 3.5, 18.1, 26.7, 72.9, 74.3, 76.4, 81.1, 127.5, 127.6 (2 C), 128.3 (2 C), 138.3.

(2*E*,4*S*)-5-(Benzyloxy)-2-iodo-4-methylpent-2-ene (9)

A soln of **24** (101 mg, 0.54 mmol) and Cp_2ZrHCl (348 mg, 1.4 mmol) in anhyd benzene (3 mL) was heated at 40 °C for 30 min. After cooling of the mixture, a soln of I_2 (274 mg, 1.1 mmol) in anhyd benzene (2 mL) was added at r.t. After 30 min, the reaction was quenched with sat. $Na_2S_2O_3$ (2 mL) at 0 °C, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed successively with 3% aq HCl (15 mL), sat. aq $NaHCO_3$ (15 mL), and brine (15 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 100:1); this gave **9**, containing an inseparable regioisomer, as a pale yellow oil.

Yield: 118 mg (70%, 13% regioisomer); $[\alpha]_D^{20}$ –12.3 (*c* 1.25, $CHCl_3$).

IR (neat): 610, 698, 735, 853, 1049, 1098, 1204, 1375, 1453, 1495, 1638, 2855, 2926, 2963, 3030 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.8 Hz, 3 H), 2.40 (s, 3 H), 2.77 (m, 1 H), 3.29 (dd, *J* = 3.4, 6.7 Hz, 2 H), 4.52 (s, 2 H), 6.00 (dd, *J* = 1.5, 9.5 Hz, 1 H), 7.25–7.37 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.0, 27.9, 36.1, 73.0, 74.2, 94.5, 127.5, 127.6, 127.6, 128.3, 138.4, 143.8.

HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}IO$: 317.0402; found: 317.0422.

(2*S*,4*R*)-5-(*tert*-Butyldiphenylsiloxy)-2,4-dimethylpentan-1-ol (26)

An O_3 stream was bubbled through a soln of **25**[23] (369 mg, 1.0 mmol) in CH_2Cl_2–MeOH (3:1, 20 mL) at –78 °C until the color of the soln had changed to blue. The mixture was purged with argon, and then $NaBH_4$ (304 mg, 8.1 mmol) in EtOH–H_2O (1:1, 15 mL) was added at –78 °C. The mixture was allowed to warm to r.t. over 1 h. The reaction was quenched with 3% aq HCl (10 mL) at 0 °C, and the mixture was extracted with CH_2Cl_2 (2 × 40 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (2 × 20 mL) and brine (20 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 1:0 to 20:1).

Yield: 315 mg (84%); colorless oil; $[\alpha]_D^{20}$ +1.74 (*c* 1.45, $CHCl_3$).

IR (neat): 505, 613, 702, 740, 1362, 1389, 1427, 1472, 1589, 1892, 1960, 2859, 2930, 2957, 3052, 3071, 3355 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.7 Hz, 3 H), 0.93 (m, 1 H), 0.95 (d, *J* = 6.7 Hz, 3 H), 1.05 (s, 9 H), 1.26 (br, 1 H), 1.46 (m, 1 H), 1.64 (m, 1 H), 1.74 (m, 1 H), 3.35 (dd, *J* = 6.7, 10.5 Hz, 1 H), 3.41 (dd, *J* = 6.3, 9.9 Hz, 1 H), 3.46 (dd, *J* = 5.1, 10.6 Hz, 1 H), 3.52 (dd, *J* = 5.4, 9.9 Hz, 1 H), 7.35–7.45 (m, 6 H), 7.63–7.69 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.4, 17.9, 19.3, 26.8 (3 C), 33.12, 33.13, 37.1, 68.3, 68.7, 127.58 (2 C), 127.59 (2 C), 129.5 (2 C), 133.94, 133.95, 135.62 (2 C), 135.63 (2 C).

HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{35}O_2Si$: 371.2406; found: 371.2432.

(2*R*,4*S*)-1-(*tert*-Butyldiphenylsiloxy)-5-iodo-2,4-dimethylpentane (10)

MsCl (0.13 mL, 1.7 mmol) was added dropwise to a stirred soln of **26** (417 mg, 1.1 mmol) in anhyd CH_2Cl_2 (6 mL) containing Et_3N (0.31 mL, 2.2 mmol) at r.t. After 1 h, the reaction was quenched with sat. aq $NaHCO_3$ (5 mL) at 0 °C, and the mixture was extracted with CH_2Cl_2 (2 × 25 mL). The combined extracts were washed successively with 3% aq HCl (15 mL), sat. aq $NaHCO_3$ (15 mL), and brine (15 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded the corresponding mesylate (515 mg) as a colorless oil, which was used for the next reaction without further purification.

A mixture of the crude mesylate (515 mg) and NaI (1.01 g, 6.7 mmol) in acetone (10 mL) was heated at reflux for 6 h. After cooling, the mixture was diluted with H_2O (5 mL), and extracted with Et_2O (3 × 30 mL). The combined extracts were washed with sat. aq $Na_2S_2O_3$ (20 mL) and brine (20 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 20:1).

Yield: 513 mg (95%, 2 steps); colorless oil; $[\alpha]_D^{20}$ +7.3 (*c* 1.42, $CHCl_3$).

IR (neat): 503, 615, 702, 739, 824, 1111, 1194, 1262, 1389, 1427, 1460, 1589, 2859, 2930, 2959, 3071 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.3 Hz, 3 H), 0.94 (d, *J* = 6.7 Hz, 3 H), 1.00 (m, 1 H), 1.06 (s, 9 H), 1.47 (m, 2 H), 1.70 (m, 1 H), 3.07 (dd, *J* = 5.9, 9.6 Hz, 1 H), 3.23 (dd, *J* = 3.6, 9.5 Hz, 1 H), 3.43 (dd, *J* = 6.1, 9.9 Hz, 1 H), 3.49 (dd, *J* = 5.5, 9.9 Hz, 1 H), 7.35–7.45 (m, 6 H), 7.66 (dd, *J* = 0.9, 6.5 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.3, 18.0, 19.3, 21.4, 26.9 (3 C), 31.8, 33.1, 40.4, 68.8, 127.6 (4 C), 129.6 (2 C), 133.9 (2 C), 135.6 (4 C).

HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{34}IOSi$: 481.1424; found: 481.1407.

(2*S*,3*E*,6*S*,8*R*)-1-(Benzyloxy)-9-(*tert*-butyldiphenylsiloxy)-2,4,6,8-tetramethylnon-3-ene (28)

A 1.0 M soln of $ZnCl_2$ in Et_2O (0.58 mL, 0.58 mmol) was added to a stirred soln of **10** (279 mg, 0.58 mmol) in anhyd Et_2O (2 mL) at r.t. For the deaeration of the reaction mixture, it was frozen in liquid N_2, and the reaction vessel was evacuated in vacuo for 30 min before being filled with dry argon (freeze–vacuum deaeration technique). A 1.41 M soln of *t*-BuLi in pentane (1.24 mL, 1.8 mmol) was added to a stirred soln of the above mixture at –78 °C over 10 min under argon. The resulting soln was gradually warmed to –40 °C and stirred for 30 min at the same temperature. The mixture was allowed to warm to r.t., and stirring was continued for 1 h. A soln of **9** (160 mg, 0.51 mmol, including 13% of an inseparable 3-iodo regioisomer) in anhyd THF (2 mL) and $Pd(PPh_3)_4$ (58.0 mg, 51 μmol) in anhyd THF (2 mL) [degassed by freeze–vacuum deaeration technique for 30 min] were added successively to the above cloudy suspension of alkylzinc reagent, and the resulting mixture was stirred for 13 h at r.t. while shielded from light. The reaction was quenched with H_2O (10 mL) at 0 °C, and the mixture was extracted with Et_2O (3 × 20 mL). The organic layer was washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–CH_2Cl_2, 4:1).

Yield: 188 mg (81%); colorless oil; $[\alpha]_D^{20}$ +11.8 (*c* 1.00, $CHCl_3$).

IR (neat): 503, 569, 613, 700, 739, 1109, 1262, 1387, 1427, 1456, 1589, 1740, 2857, 2928, 2959, 3071 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.74 (d, *J* = 6.1 Hz, 3 H), 0.92 (d, *J* = 6.7 Hz, 3 H), 0.97 (d, *J* = 6.7 Hz, 3 H), 1.05 (s, 9 H), 1.20–1.35 (m, 2 H), 1.56 (d, *J* = 1.2 Hz, 3 H), 1.58–1.65 (m, 2 H), 1.75 (m, 1 H), 2.00 (m, 1 H), 2.71 (m, 1 H), 3.22 (dd, *J* = 7.6, 9.1 Hz, 1 H), 3.32 (dd, *J* = 6.1, 9.1 Hz, 1 H), 3.40 (dd, *J* = 6.6, 9.8 Hz, 1 H), 3.50 (dd, *J* = 5.2, 9.8 Hz, 1 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 4.47 (d, *J* = 12.1 Hz, 1 H), 4.90 (d, *J* = 9.0 Hz, 1 H), 7.26–7.45 (m, 11 H), 7.67 (dd, *J* = 1.4, 7.9 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.2, 17.8, 18.0, 19.3, 19.8, 26.9 (3 C), 28.1, 33.0, 33.2, 41.4, 47.7, 69.0, 72.9, 75.5, 127.4, 127.5 (2 C), 127.6 (4 C), 128.3 (2 C), 128.9, 129.5 (2 C), 134.12, 134.13, 134.5, 135.62 (2 C), 135.64 (2 C), 138.8.

HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{36}H_{51}O_2Si$: 543.3658; found: 543.3640.

(2*S*,3*E*,6*S*,8*R*)-9-(*tert*-Butyldiphenylsiloxy)-2,4,6,8-tetramethylnon-3-en-1-ol (29)

A 0.26 M soln of LiDBB in THF (4.0 mL, 1.1 mmol) [prepared from Li (8.7 mg, 1.3 mmol) and DTBB (346 mg, 1.3 mmol)] was added dropwise to a stirred soln of **28** (40.0 mg, 70 μmol) in anhyd THF (1.5 mL) at –78 °C. After 5 min, the reaction was quenched with brine (5 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (2 × 20 mL). The combined extracts were washed with brine (2 × 10 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 10:1).

Yield: 30.0 mg (90%); pale yellow oil; $[\alpha]_D^{20}$ –7.73 (*c* 1.00, $CHCl_3$).

IR (neat): 505, 615, 702, 741, 824, 939, 1032, 1111, 1188, 1260, 1387, 1427, 1460, 1589, 2859, 2928, 2957, 3362 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.0 Hz, 3 H), 0.92 (d, *J* = 6.7 Hz, 3 H), 0.94 (d, *J* = 6.7 Hz, 3 H), 1.05 (s, 9 H), 1.32 (m, 2 H), 1.53 (s, 1 H), 1.58 (d, *J* = 1.2 Hz, 3 H), 1.60–1.68 (m, 2 H), 1.77 (m, 1 H), 2.04 (dd, *J* = 9.7, 17.3 Hz, 1 H), 2.60 (m, 1 H), 3.25–3.55 (m, 4 H), 4.85 (d, *J* = 9.4 Hz, 1 H), 7.35–7.45 (m, 6 H), 7.67 (dd, *J* = 1.4, 7.9 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4, 17.1, 17.8, 19.3, 19.8, 26.9 (3 C), 28.1, 33.2, 35.5, 41.5, 47.8, 68.0, 69.0, 127.6 (4 C), 128.5, 129.5 (2 C), 134.09, 134.10, 135.6 (4 C), 136.8.

HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{45}O_2Si$: 453.3189; found: 453.3189.

(3*R*,4*E*,7*S*,9*R*)-10-(*tert*-Butyldiphenylsiloxy)-3,5,7,9-tetramethyldec-4-ene (30)

TsCl (63.0 mg, 0.33 mmol) was added to a stirred soln of **29** (51.0 mg, 0.11 mmol) in anhyd CH_2Cl_2 (0.9 mL) containing Et_3N (0.14 mL, 0.99 mmol) and DMAP (1.3 mg, 11 μmol) at r.t. After 3 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL), and the organic layer was washed successively with 3% aq HCl (2 × 10 mL), sat. aq $NaHCO_3$ (2 × 10 mL), and brine (10 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded the corresponding tosylate **8** (80 mg) as a pale yellow oil, which was used for the next reaction without further purification.

A 1.2 M soln of MeLi in Et_2O (5.50 mL, 6.6 mmol) was added dropwise to a stirred suspension of CuI (628 mg, 3.3 mmol) in anhyd Et_2O (3 mL) at –10 °C under argon. After 30 min, a soln of the crude tosylate **8** (80 mg) in anhyd Et_2O (5 mL) was added to the above mixture at –40 °C. The resulting mixture was allowed to warm to r.t., and stirring was continued for 13 h. The reaction was quenched with 25% NH_4OH (3 mL) and sat. aq NH_4Cl (3 mL) at 0 °C, and then the resulting mixture was stirred under air until the color of the soln had changed to bright blue. The mixture was extracted with Et_2O (2 × 20 mL), and the combined extracts were washed with brine (2 × 10 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane).

Yield: 49.2 mg (97%, 2 steps); pale yellow oil; $[\alpha]_D^{20}$ –5.22 (*c* 1.18, $CHCl_3$).

IR (neat): 503, 615, 702, 738, 822, 1111, 1262, 1385, 1427, 1460, 2859, 2928, 2959 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.75 (d, *J* = 6.1 Hz, 3 H), 0.81 (t, *J* = 7.4 Hz, 3 H), 0.89 (d, *J* = 6.7 Hz, 3 H), 0.94 (d, *J* = 6.7 Hz, 3 H), 1.05 (s, 9 H), 1.13–1.23 (m, 2 H), 1.27–1.39 (m, 2 H), 1.52 (d, *J* = 1.3 Hz, 3 H), 1.56–1.65 (m, 2 H), 1.75 (m, 1 H), 1.97 (dd, *J* = 9.3, 16.8 Hz, 1 H), 2.22 (m, 1 H), 3.40 (dd, *J* = 6.6, 9.8 Hz, 1 H), 3.56 (dd, *J* = 5.1, 9.8 Hz, 1 H), 4.83 (d, *J* = 9.3 Hz, 1 H), 7.34–7.44 (m, 6 H), 7.66 (dd, *J* = 1.3, 7.7 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.0, 16.2, 17.9, 19.3, 20.0, 21.0, 26.9 (3 C), 28.2, 30.5, 33.2, 34.1, 41.3, 47.9, 69.0, 127.6 (4 C), 129.46, 129.47, 132.3, 132.9, 134.14, 134.16, 135.63 (2 C), 135.65 (2 C).

HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{47}OSi$: 451.3396; found: 451.3412.

(2*R*,4*S*,6*E*,8*R*)-2,4,6,8-Tetramethyldec-6-en-1-ol (31)

A 1.0 M soln of TBAF in THF (0.61 mL, 0.61 mmol) was added to a stirred soln of **30** (91.7 mg, 0.20 mmol) in THF (1.5 mL) at r.t. After 24 h, the reaction mixture was diluted with Et_2O (30 mL), and the organic layer was washed with sat. aq $NaHCO_3$ (10 mL) and brine (10 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 20:1).

Yield: 39.5 mg (91%); colorless oil; $[\alpha]_D^{20}$ –9.23 (*c* 1.20, $CHCl_3$).

IR (neat): 511, 608, 702, 818, 880, 1036, 1111, 1260, 1377, 1458, 1547, 1669, 1725, 2276, 2870, 2922, 2957, 3353 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 7.5 Hz, 3 H), 0.84 (t, *J* = 7.4 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H), 0.94 (d, *J* = 6.7 Hz, 3 H), 1.15–1.25 (m, 2 H), 1.25–1.38 (m, 3 H), 1.56 (d, *J* = 1.4 Hz, 3 H), 1.64–1.70 (m, 2 H), 1.75 (m, 1 H), 2.00 (dd, *J* = 9.4, 17.1 Hz, 1 H), 2.24 (m, 1 H), 3.37 (dd, *J* = 6.9, 10.4 Hz, 1 H), 3.53 (dd, *J* = 5.0, 10.5 Hz, 1 H), 4.86 (d, *J* = 9.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.0, 16.2, 17.5, 20.2, 21.0, 28.2, 30.5, 33.2, 34.1, 40.9, 47.7, 68.3, 132.2, 133.1.

HRMS–FAB: *m*/*z* $[M]^+$ calcd for $C_{14}H_{28}O$: 212.2140; found: 212.2131.

Methyl (2*E*,4*E*,6*E*,8*R*,10*S*,12*E*,14*R*)-8,10,12,14-Tetramethylhexadeca-2,4,6,12-tetraenoate (34)

A mixture of **31** (39.5 mg, 0.19 mmol), 3-Å MS (33 mg), and NMO (76.0 mg, 0.65 mmol) in CH_2Cl_2 (2.8 mL) was stirred for 10 min at r.t. *n*-Pr_4NRuO_4 (13.0 mg, 37 μmol) was added to the above mixture at r.t. After 10 min, the mixture was filtered through a short pad of silica gel, and the filtrate was concentrated in vacuo (water bath < 25°C); this gave aldehyde **32** (26.1 mg) as a colorless oil, which was used immediately for the next reaction.

A soln of **33**[29] (76.0 mg, 0.32 mmol) in anhyd THF (0.7 mL) was added dropwise to a stirred soln of LDA in anhyd THF [prepared from *i*-Pr_2NH (50.0 μL, 0.32 mmol) and 1.58 M *n*-BuLi in *n*-hexane (0.20 mL, 0.32 mmol) in THF (0.34 mL)] at –78 °C. After 30 min, a soln of the crude aldehyde **32** (26.1 mg) in anhyd THF (0.7 mL) was added slowly to the above soln, and the resulting mixture was stirred for 30 min at –78 °C and for 30 min at –30 °C. The reaction was quenched with sat. aq NH_4Cl (5 mL) at –30 °C, and the resulting mixture was extracted with Et_2O (2 × 30 mL). The combined extracts were washed with brine (2 × 15 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue,

which was purified by column chromatography (hexane–EtOAc, 100:1); this gave a mixture of **34** and its 6′*Z*-isomer (49.2 mg, 82%; ratio 73:27, by 500-MHz ^{1}H NMR). A pure sample of **34** was isolated from this mixture by HPLC [DAICEL CHIRALPAK AD-H, i.d. 10 × 250 mm; hexane–*i*-PrOH, 200:1, 1.0 mL·min^{-1}; UV detection: 254 nm absorbance; t_R (**34**): 12.5 min, t_R (6′*Z*-isomer): 10.8 min].

Yield: 27.2 mg (46%, 2 steps); colorless oil; $[\alpha]_D^{20}$ –1.57 (*c* 1.45, $CHCl_3$).

IR (neat): 505, 613, 702, 740, 1362, 1389, 1427, 1472, 1589, 1892, 1960, 2859, 2930, 2957, 3052, 3071, 3355 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.5 Hz, 3 H), 0.84 (d, *J* = 7.4 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 1.02 (m, 1 H), 1.19 (m, 1 H), 1.27–1.39 (m, 2 H), 1.52 (d, *J* = 1.2 Hz, 3 H), 1.56 (m, 1 H), 1.76 (dd, *J* = 7.3, 13.2 Hz, 1 H), 1.88 (dd, *J* = 6.8, 13.1 Hz, 1 H), 2.23 (m, 1 H), 2.34 (m, 1 H), 3.74 (s, 3 H), 4.85 (d, *J* = 9.4 Hz, 1 H), 5.73 (dd, *J* = 8.5, 15.2 Hz, 1 H), 5.84 (d, *J* = 15.3 Hz, 1 H), 6.10 (dd, *J* = 10.7, 15.2 Hz, 1 H), 6.22 (dd, *J* = 11.3, 14.9 Hz, 1 H), 6.52 (dd, *J* = 10.7, 14.9 Hz, 1 H), 7.31 (dd, *J* = 11.3, 15.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.1, 16.2, 19.5, 21.1, 21.4, 28.4, 30.6, 34.1, 35.0, 44.0, 48.3, 51.5, 119.5, 127.8, 128.2, 132.1, 133.1, 141.5, 145.1, 146.5, 167.7.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{34}O_2$: 319.2637; found: 319.2623.

(2*E*,4*E*,6*E*,8*R*,10*S*,12*E*,14*R*)-8,10,12,14-Tetramethylhexadeca-2,4,6,12-tetraenoyl Chloride (3)

A soln of **34** (26.2 mg, 82 μmol) in 2 M aq KOH–THF–MeOH (3:3:1, 2 mL) was stirred for 12 h at r.t. The reaction mixture was acidified with 1 M HCl (2 mL) at 0 °C and extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$). Concentration of the soln in vacuo afforded carboxylic acid **35** (26.0 mg), which was used for the following reaction without further purification.

Oxalyl chloride (21.0 μL, 0.24 mmol) was added to a stirred soln of the crude carboxylic acid **35** (26.0 mg) in CH_2Cl_2 (2 mL) containing DMF (6.0 μL, 82 μmol) at r.t. After 1 h, the solvent was removed in vacuo; this afforded acid chloride **3** (26.0 mg) as a colorless oil, which was used immediately, without further purification, for the next reaction.

(2*E*,4*E*,6*E*,8*R*,10*S*,12*E*,14*R*)-*N*-{(1*S*)-2-[(3a*S*,4*R*,7*R*,7a*S*)-4-(*tert*-Butyldimethylsiloxy)-7-hydroxy-2,2-dimethyl-7,7a-dihydro-1,3-benzodioxol-3a(4*H*)-yl]-1-(hydroxymethyl)ethyl}-8,10,12,14-tetramethylhexadeca-2,4,6,12-tetraenamide (37)

TMSOTf (0.26 mL, 1.4 mmol) was added dropwise to a stirred soln of **2** (32.0 mg, 54 μmol) in anhyd CH_2Cl_2 (2 mL) containing 2,6-lutidine (0.28 mL, 2.4 mmol) at 0 °C. The soln was stirred for 3 h at r.t. MeOH (2 mL) was added, and stirring was continued for 1 h at r.t. The mixture was diluted with H_2O (5 mL), and extracted with Et_2O (5 × 30 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (30 mL) and brine (30 mL), and then dried (Na_2SO_4). Concentration of the soln in vacuo afforded amino alcohol **36** (80 mg, containing a small amount of 2,6-lutidine), which was used for the next reaction without further purification.

A soln of crude acid chloride **3** (26.0 mg, ca. 80 μmol) in anhyd CH_2Cl_2 (2 mL) was added dropwise to a stirred soln of the crude amino alcohol **36** (80.0 mg, containing a small amount of 2,6-lutidine) in anhyd CH_2Cl_2 (2 mL) containing Et_3N (80 μL, 0.58 mmol) at r.t. After 1 h, 60% aq AcOH (1.0 mL) was added, and the soln was stirred for 6 h at r.t. The mixture was diluted with H_2O (15 mL) and then extracted with Et_2O (2 × 50 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (30 mL) and brine (30 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue of **37**, which was purified by column chromatography (hexane–EtOAc, 2:1 to 1:1).

Yield: 26.0 mg (73%); colorless oil; $[\alpha]_D^{20}$ –33.7 (*c* 0.97, $CHCl_3$).

IR (neat): 777, 837, 1062, 1251, 1375, 1460, 1543, 1609, 1649, 2928, 2957, 3040, 3285 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.07 (s, 6 H), 0.80 (d, *J* = 6.5 Hz, 3 H), 0.84 (t, *J* = 7.4 Hz, 3 H), 0.88 (s, 9 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 1.03 (m, 1 H), 1.20 (dt, *J* = 13.4, 7.7 Hz, 1 H), 1.27–1.36 (m, 2 H), 1.44 (s, 3 H), 1.48 (s, 3 H), 1.52 (s, 3 H), 1.56 (m, 1 H), 1.76 (dd, *J* = 7.4, 15.0 Hz, 1 H), 1.81–1.91 (m, 2 H), 1.93 (dd, *J* = 6.3, 15.0 Hz, 1 H), 2.23 (m, 1 H), 2.33 (m, 1 H), 2.41 (br, 1 H), 3.06 (br, 1 H), 3.68 (br d, *J* = 9.0 Hz, 1 H), 3.85 (dd, *J* = 4.0, 11.4 Hz, 1 H), 3.90 (d, *J* = 4.4 Hz, 1 H), 4.17 (m, 1 H), 4.31 (d, *J* = 5.2 Hz, 1 H), 4.72 (m, 1 H), 4.84 (br d, *J* = 9.3 Hz, 1 H), 5.70 (dd, *J* = 8.4, 15.2 Hz, 1 H), 5.77 (d, *J* = 14.9 Hz, 1 H), 5.87–5.94 (m, 2 H), 6.05–6.13 (m, 2 H), 6.18 (dd, *J* = 11.3, 14.8 Hz, 1 H), 6.49 (dd, *J* = 10.7. 14.8 Hz, 1 H), 7.23 (dd, *J* = 11.3, 14.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.5, –4.1, 12.1, 16.2, 18.2, 19.5, 21.1, 21.4, 26.0 (3 C), 27.5 (2 C), 28.3, 30.5, 34.1, 35.0, 41.9, 44.0, 48.3, 48.6, 65.5, 67.4, 70.7, 83.9, 86.9, 110.7, 122.1, 127.7, 128.3, 131.9, 132.1, 133.1, 133.7, 140.6, 141.8, 145.7, 166.1.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{38}H_{66}NO_6Si$: 660.4659; found: 660.4642.

(2*E*,4*E*,6*E*,8*R*,10*S*,12*E*,14*R*)-*N*-{(1*S*)-1-(Acetoxymethyl)-2-[(3a*S*,4*R*,7*R*,7a*S*)-4-(*tert*-butyldimethylsiloxy)-7-hydroxy-2,2-dimethyl-7,7a-dihydro-1,3-benzodioxol-3a(4*H*)-yl]ethyl}-8,10,12,14-tetramethylhexadeca-2,4,6,12-tetraenamide (38)

A soln of Ac_2O (5.4 μL, 52 μmol) in CH_2Cl_2 (0.2 mL) was added to a stirred soln of **37** (34.0 mg, 52 μmol) in CH_2Cl_2 (1.6 mL) containing py (20 μL, 0.24 mmol) and DMAP (0.4 mg, 3.2 μmol) at r.t. After 20 min, the mixture was diluted with H_2O (5 mL), and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (2 × 15 mL) and brine (15 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 5:1).

Yield: 26.0 mg [72%, or 81% based on recovered **37** (4.0 mg, 12%)]; colorless oil; $[\alpha]_D^{20}$ –26.5 (*c* 0.96, $CHCl_3$).

IR (neat): 777, 837, 1061, 1250, 1371, 1460, 1539, 1610, 1649, 1744, 2928, 2957, 3055, 3281 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.09 (s, 6 H), 0.80 (d, *J* = 6.5 Hz, 3 H), 0.84 (t, *J* = 7.4 Hz, 3 H), 0.88 (s, 9 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 1.02 (m, 1 H), 1.19 (dt, *J* = 13.4, 7.8 Hz, 1 H), 1.27–1.35 (m, 2 H), 1.38 (s, 3 H), 1.44 (s, 3 H), 1.52 (d, *J* = 1.2 Hz, 3 H), 1.56 (m, 1 H), 1.73–1.81 (m, 2 H), 1.85–1.91 (m, 2 H), 2.07 (s, 3 H), 2.23 (m, 1 H), 2.33 (m, 1 H), 2.41 (m, 1 H), 3.87 (d, *J* = 4.6 Hz, 1 H), 4.21 (d, *J* = 3.8, 11.3 Hz, 1 H), 4.33 (dd, *J* = 6.0, 11.3 Hz, 1 H), 4.41–4.49 (m, 2 H), 4.68 (br s, 1 H), 4.84 (d, *J* = 9.4 Hz, 1 H), 5.65–5.80 (m, 2 H), 5.75 (d, *J* = 14.9 Hz, 1 H), 5.87 (dd, *J* = 2.7, 9.6 Hz, 1 H), 6.04–6.12 (m, 2 H), 6.18 (dd, *J* = 11.3, 14.8 Hz, 1 H), 6.49 (dd, *J* = 10.7, 14.8 Hz, 1 H), 7.23 (dd, *J* = 11.3, 14.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.5, –4.1, 12.1, 16.2, 18.2, 19.5, 20.9, 21.1, 21.4, 26.0 (3 C), 27.5, 27.6, 28.3, 30.5, 34.1, 35.0, 42.6, 44.0, 46.1, 48.3, 66.6, 67.3, 70.7, 84.0, 87.1, 110.6, 122.0, 127.7, 128.3, 132.1, 132.6, 133.1, 133.1, 140.7, 141.9, 145.8, 165.6, 171.4.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{40}H_{68}NO_7Si$: 702.4765; found: 702.4748.

(2*E*,4*E*,6*E*,8*R*,10*S*,12*E*,14*R*)-*N*-{(1*S*)-1-(Acetoxymethyl)-2-[(3a*S*,4*R*,7*R*,7a*S*)-4-(*tert*-butyldimethylsiloxy)-7-mesyloxy-2,2-dimethyl-7,7a-dihydro-1,3-benzodioxol-3a(4*H*)-yl]ethyl}-8,10,12,14-tetramethylhexadeca-2,4,6,12-tetraenamide (39)

MsCl (8.0 μL, 0.1 mmol) was added to a stirred soln of **38** (31.0 mg, 38 μmol) in CH_2Cl_2 (2 mL) containing Et_3N (82.0 μL, 0.60 mmol) at r.t. After 1 h, the reaction was quenched with H_2O (2 mL), and the mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with 1 M HCl (2 × 10 mL), sat. aq $NaHCO_3$ (2 × 10 mL), and brine (10 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 6:1).

Yield: 32.0 mg (93%); colorless oil; $[\alpha]_D^{20}$ –31.2 (*c* 1.07, $CHCl_3$).

IR (neat): 777, 841, 1078, 1177, 1250, 1364, 1460, 1539, 1611, 1649, 1744, 2928, 2957, 3045, 3271 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.09 (s, 3 H), 0.10 (s, 3 H), 0.80 (d, *J* = 6.5 Hz, 3 H), 0.84 (t, *J* = 7.4 Hz, 3 H), 0.89 (s, 9 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 1.00 (d, *J* = 6.6 Hz, 3 H), 1.02 (m, 1 H), 1.19 (dt, *J* = 13.4, 7.8 Hz, 1 H), 1.27–1.35 (m, 2 H), 1.38 (s, 3 H), 1.47 (s, 3 H), 1.52 (d, *J* = 1.0 Hz, 3 H), 1.56 (m, 1 H), 1.73–1.81 (m, 2 H), 1.81–1.91 (m, 2 H), 2.08 (s, 3 H), 2.23 (m, 1 H), 2.33 (m, 1 H), 3.10 (s, 3 H), 3.99 (d, *J* = 4.9 Hz, 1 H), 4.22 (dd, *J* = 3.7, 11.3 Hz, 1 H), 4.34 (dd, *J* = 5.8, 11.3 Hz, 1 H), 4.43 (m, 1 H), 4.50 (d, *J* = 5.4 Hz, 1 H), 4.84 (d, *J* = 9.3 Hz, 1 H), 5.52 (m, 1 H), 5.65–5.75 (m, 2 H), 5.75 (d, *J* = 15.1 Hz, 1 H), 5.93 (dd, *J* = 2.4, 9.7 Hz, 1 H), 6.08 (dd, *J* = 10.7, 15.1 Hz, 1 H), 6.17 (dd, *J* = 11.3, 14.8 Hz, 1 H), 6.25 (m, 1 H), 6.49 (dd, *J* = 10.7. 14.8 Hz, 1 H), 7.21 (dd, *J* = 11.3, 14.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.6, –4.2, 12.1, 16.2, 18.2, 19.5, 20.9, 21.1, 21.4, 26.0 (3 C), 27.4, 27.6, 28.3, 30.6, 34.1, 35.0, 38.4, 42.5, 44.0, 46.1, 48.3, 66.4, 66.8, 80.8, 83.8, 84.1, 111.5, 121.9, 127.6, 128.3, 129.2, 132.1, 133.1, 134.7, 140.7, 141.9, 145.8, 165.5, 171.3.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{41}H_{70}NO_9SSi$: 780.4541; found: 780.4541.

[(2*E*,4*E*,6*E*,8*R*,10*S*,12*E*,14*R*)-*N*-{(1*S*)-1-(Acetoxymethyl)-2-[(3a*S*,7*R*,7a*S*)-7-mesyloxy-2,2-dimethyl-4-oxo-7,7a-dihydro-1,3-benzodioxol-3a(4*H*)-yl]ethyl}-8,10,12,14-tetramethylhexadeca-2,4,6,12-tetraenamide (40)

A 1 M soln of TBAF in THF (30.0 μL, 30 μmol) was added to a stirred soln of **39** (24.0 mg, 30 μmol) in THF (1.5 mL) at r.t. After 30 min, additional 1 M TBAF in THF (20.0 μL, 20 μmol) was added. After 20 min, the mixture was diluted with Et_2O (30 mL), and the organic layer was washed with 1 M NaOH (8 mL) and brine (8 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded the corresponding alcohol (22.0 mg) as a colorless oil, which was used for the next reaction without further purification.

DMP (48.0 mg, 0.11 mmol) was added to a stirred soln of the crude alcohol (22.0 mg) in CH_2Cl_2 (2 mL) at r.t. After 20 min, the reaction was quenched with 15% aq $Na_2S_2O_3$ (2 mL) at 0 °C, and the mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with 1 M NaOH (10 mL) and brine (10 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 6:1 to 2:1).

Yield: 20.0 mg (98%, 2 steps); colorless oil; $[\alpha]_D^{20}$ –21.8 (*c* 0.98, $CHCl_3$).

IR (neat): 794, 858, 1071, 1177, 1237, 1368, 1457, 1534, 1611, 1653, 1696, 1741, 2926, 2959, 3378 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.5 Hz, 3 H), 0.84 (t, *J* = 7.4 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 1.02 (m, 1 H), 1.19 (dt, *J* = 13.4, 7.8 Hz, 1 H), 1.26 (s, 3 H), 1.27–1.35 (m, 2 H), 1.33 (s, 3 H), 1.52 (d, *J* = 1.0 Hz, 3 H), 1.56 (m, 1 H), 1.76 (dd, *J* = 7.4, 13.1 Hz, 1 H), 1.85–1.94 (m, 2 H), 2.06 (s, 3 H), 2.20 (dd, *J* = 9.2, 15.6 Hz, 1 H), 2.23 (m, 1 H), 2.33 (m, 1 H), 3.22 (s, 3 H), 4.10 (dd, *J* = 4.8, 11.3 Hz, 1 H), 4.23 (dd, *J* = 5.1, 11.3 Hz, 1 H), 4.42–4.50 (m, 2 H), 4.84 (d, *J* = 9.5 Hz, 1 H), 5.52 (dd, *J* = 1.7, 3.8 Hz, 1 H), 5.71 (dd, *J* = 8.4, 15.2 Hz, 1 H), 5.75 (d, *J* = 15.0 Hz, 1 H), 5.84 (d, *J* = 7.6 Hz, 1 H), 6.08 (dd, *J* = 10.8, 15.0 Hz, 1 H), 6.18 (dd, *J* = 11.3, 14.9 Hz, 1 H), 6.26 (d, *J* = 10.1 Hz, 1 H), 6.48 (dd, *J* = 10.7, 14.8 Hz, 1 H), 6.83 (ddd, *J* = 1.9, 4.8, 10.1 Hz, 1 H), 7.21 (dd, *J* = 11.3, 14.9 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.1, 16.2, 19.5, 20.8, 21.1, 21.4, 26.7, 27.1, 28.4, 29.7, 30.5, 34.1, 35.0, 39.0, 44.0, 45.4, 48.3, 66.1, 70.6, 77.7, 81.1, 110.0, 122.0, 127.6, 128.2, 130.5, 132.1, 133.1, 138.9, 140.8, 141.9, 145.9, 165.7, 171.0, 197.2.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{54}NO_9S$: 664.3519; found: 664.3544.

(2*E*,4*E*,6*E*,8*R*,10*S*,12*E*,14*R*)-*N*-[(1*S*)-2-Acetoxy-1-{[(1*S*,2*S*,3*S*)-2,3-epoxy-1-hydroxy-6-oxocyclohex-4-enyl]methyl}ethyl]-8,10,12,14-tetramethylhexadeca-2,4,6,12-tetraenamide (41)

A soln of **40** (6.6 mg, 6.9 μmol) and Cl_3CCO_2H (66.0 mg, 0.42 mmol) in CH_2Cl_2 (0.36 mL) containing H_2O (18 μL) was heated at reflux for 3 h. The mixture was basified with 2 M NaOH (0.22 mL) at 0 °C, and the resulting mixture was stirred for 10 min at r.t. The mixture was diluted with H_2O (8 mL), and extracted with Et_2O (3 × 30 mL). The combined extracts were washed with brine (2 × 20 mL) and dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (hexane–EtOAc, 2:1 to 1:3).

Yield: 2.4 mg [45%, or 82% based on recovered **40** (3.0 mg, 45%)]; colorless oil; $[\alpha]_D^{20}$ +46.9 (*c* 0.12, $CHCl_3$).

IR (neat): 736, 837, 1006, 1238, 1373, 1456, 1539, 1609, 1651, 1682, 1732, 2924, 2959, 3353 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.5 Hz, 3 H), 0.84 (t, *J* = 7.4 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 0.99 (d, *J* = 6.7 Hz, 3 H), 1.02 (m, 1 H), 1.19 (m, 1 H), 1.27–1.35 (m, 2 H), 1.52 (d, *J* = 1.3 Hz, 3 H), 1.76 (dd, *J* = 7.3, 13.0 Hz, 1 H), 1.87 (dd, *J* = 7.1, 13.0 Hz, 1 H), 1.96–2.10 (m, 3 H), 2.07 (s, 3 H), 2.23 (m, 1 H), 2.33 (m, 1 H), 3.58 (dt, *J* = 1.6, 3.9 Hz, 1 H), 3.72 (d, *J* = 3.8 Hz, 1 H), 4.02 (m, 1 H), 4.14 (m, 1 H), 4.22–4.32 (m, 2 H), 4.83 (d, *J* = 9.4 Hz, 1 H), 5.71 (dd, *J* = 8.4, 15.4 Hz, 1 H), 5.73 (d, *J* = 15.0 Hz, 1 H), 5.86 (d, *J* = 7.1 Hz, 1 H), 6.08 (dd, *J* = 10.8, 15.1 Hz, 1 H), 6.17 (dd, *J* = 11.3, 15.0 Hz, 1 H), 6.23 (dd, *J* = 1.6, 9.9 Hz, 1 H), 6.49 (dd, *J* = 10.6. 14.8 Hz, 1 H), 7.13 (dd, *J* = 3.9, 9.9 Hz, 1 H), 7.23 (dd, *J* = 11.4, 14.9 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.1, 16.2, 19.5, 20.8, 21.1, 21.4, 28.3, 30.5, 34.1, 35.0, 37.6, 44.0, 45.6, 48.0, 48.3, 55.8, 65.9, 76.6, 121.7, 127.1, 128.3, 130.1, 132.1, 133.1, 140.9, 142.1, 144.7, 145.9, 166.1, 171.1, 197.6.

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{46}NO_6$: 528.3325; found: 528.3333.

(2*E*,4*E*,6*E*,8*R*,10*S*,12*E*,14*R*)-*N*-[(1*S*)-1-{[(1*S*,2*S*,3*S*)-2,3-Epoxy-1-hydroxy-6-oxocyclohex-4-enyl]methyl}-2-hydroxyethyl]-8,10,12,14-tetramethylhexadeca-2,4,6,12-tetraenamide [(+)-scyphostatin; 1]

A mixture of **41** (3.2 mg, 6.0 μmol) and lipase PS (16 mg) in acetone (0.16 mL) containing phosphate buffer (pH 7) (0.16 mL) was stirred for 10 h at r.t. The reaction mixture was diluted with Et_2O (50 mL), and the resulting mixture was filtered through a small pad of Celite. The filtrate was washed with sat. aq $NaHCO_3$ (10 mL) and brine (10 mL), and then dried ($MgSO_4$). Concentration of the soln in vacuo afforded a residue, which was purified by column chromatography (acetone–EtOAc, 1:4). The ^1H NMR and ^{13}C NMR, IR, and HRMS–FAB spectra (see below) are compatible with those of natural (+)-scyphostatin (**1**).

Yield: 1.8 mg (60%); colorless amorphous powder; $[\alpha]_D^{25}$ +61.0 (*c* 0.08, MeOH) [lit.[1] $[\alpha]_D^{25}$ +66.4 (*c* 0.09, MeOH)].

IR (neat): 802, 1039, 1261, 1377, 1460, 1543, 1609, 1651, 1703, 1738, 2924, 2957, 3346 cm^{-1}.

^1H NMR (500 MHz, CD_3OD) δ = 0.83 (d, *J* = 6.5 Hz, 3 H), 0.86 (t, *J* = 7.4 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 1.03 (m, 1 H), 1.19 (m, 1 H), 1.33–1.38 (m, 2 H), 1.59 (d, *J* = 1.3 Hz, 3 H), 1.59 (m, 1 H), 1.79 (m, 1 H), 1.85–1.91 (m, 2 H), 2.08 (dd, *J* = 3.4, 14.7 Hz, 1 H), 2.27 (m, 1 H), 2.35 (m, 1 H), 3.46 (dd, *J* = 5.7, 10.9 Hz, 1 H), 3.52 (dd, *J* = 5.1, 10.9 Hz, 1 H), 3.59 (dt, *J* = 1.6, 3.9 Hz, 1 H), 3.67 (d, *J* = 3.9 Hz, 1 H), 4.06 (m, 1 H), 4.85 (m, 1 H), 5.70 (dd, *J* = 8.7, 15.1 Hz, 1 H), 5.90 (d, *J* = 15.0 Hz, 1 H), 6.07 (dd, *J* = 1.6, 9.9 Hz, 1 H), 6.15 (dd, *J* = 10.7, 15.1 Hz, 1 H), 6.25 (dd, *J* = 11.1, 14.9 Hz, 1 H), 6.53 (dd, *J* = 10.6, 14.7 Hz, 1 H), 7.12–7.17 (m, 2 H).

^{13}C NMR (125 MHz, CD_3OD) δ = 13.0, 16.9, 20.4, 22.0, 22.4, 30.0, 32.2, 35.9, 36.8, 40.3, 45.7, 48.5, 49.8, 50.1, 58.7, 66.1, 78.0, 124.2, 129.9, 130.4, 132.5, 134.0, 134.7, 141.9, 142.9, 146.3, 146.7, 169.1, 200.1.

HRMS–FAB: *m/z* $[M + H]^+$ calcd for $C_{29}H_{44}NO_5$: 486.3220; found: 486.3194.

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