

Headline Articles

Total Synthesis of (+)-Myriocin and (−)-Sphingofungin E from Aldohexoses Using Overman Rearrangement as the Key Reaction

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Total synthesis starting from aldohexoses of naturally occurring α-substituted α-amino acids, (+)-myriocin (**1**) and (−)-sphingofungin E (**2**), is described. Overman rearrangement of allylic trichloroacetimidate **6*E*** derived from D-mannose effectively generated the tetrasubstituted carbon with nitrogen, and subsequent Wittig olefination afforded the highly functionalized moiety **3** of myriocin stereoselectively. Sulfone-mediated coupling reaction of the allyl bromide **3** with C_{12} hydrophobic part **4** successfully constructed the carbon framework possessing *E*-olefin **28**. Removal of the sulfone and protecting groups completed the chiral and stereoselective total synthesis of (+)-myriocin (**1**). A similar transformation starting from D-glucose also accomplished the total synthesis of (−)-sphingofungin E (**2**).

Recently, a large number of α-substituted α-amino acids (an α-hydrogen atom of an α-amino acid is replaced with an alkyl substituent) derivatives, such as myriocin,[1,2] sphingofungins[3,4] and lactacystin,[5,6] have been discovered in microorganisms or marine creatures (Fig. 1). These natural products, reported to possess intriguing biological activities, have attracted considerable attention from many chemists and biologists.

Myriocin[1a] (also known as thermozymocidin[1b]) (**1**) is an antifungal agent isolated from culture broth of *Myriococcum albomyces*[1a] and *Myceria sterilia*[1b] in 1972. Later, a novel potent immunosuppresant ISP-I,[1c] isolated from *Isalia sinclairii* (ATC 24400) in 1994, was found to be identical with myriocin. This compound is reported to show the inhibitory activity against T cell proliferation and to be a remarkable immunosuppressive agent[7a] with potency equivalent to and 10- to 100-fold higher than those of clinically used FK506 and cyclosporin A, respectively. Sphingofungin E (**2**) and F, isolated from fermentation of *Paecilomyces variotii* (ATCC 74097 = MF 5537) by Merck in 1992[3b] as antifungal agents, are reported to be inhibitors of the biosynthesis of sphingolipids, inducing apoptosis in both yeast and mammalian cells. These effects are due to their potent inhibitory activities against serine palmitoyltransferase (SPT), an essential enzyme involved in the first step of sphingosine biosynthesis.[7b] Although an immunosuppressive activity of **2** has not been reported, it is anticipated that **2** has such activity as potently as myriocin.[1c] Because of their potent activities and new modes of action, myriocin and sphingofungin E as well as their derivatives are expected to be promising lead compounds for novel therapeutic agents on the basis of modulation of sphingolipid biosynthesis.[7]

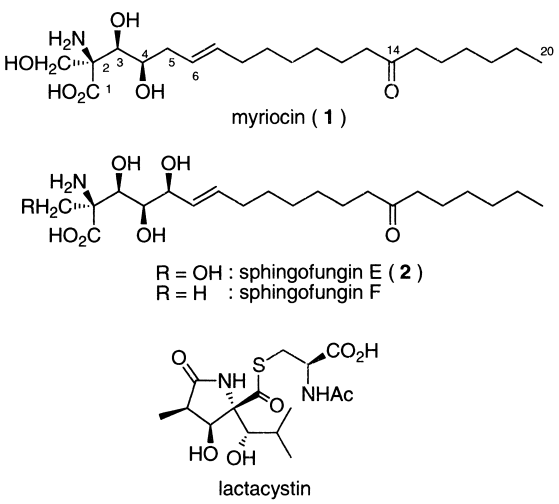


Fig. 1. Natural α-substituted α-amino acid derivatives.

These interesting biological findings and architecturally novel structures have stimulated a number of synthetic efforts, and several total syntheses and synthetic approaches have been reported.[2,4h–j] Structural features of **1** and **2** are the unusual α-substituted serine framework with *E*-olefin and three or four contiguous chiral centers including a tetrasubstituted carbon with nitrogen. For a construction of the tetrasubstituted carbon, Payette and Just employed Strecker synthesis and they synthesized an antipode of anhydromyriocin (γ-lactone derivative of myriocin) from L-arabinose.[2a] Scolastico's group succeeded in the first total synthesis of **1**, in which they construct-

ed the tetrasubstituted carbon by hydrocyanation of an imine derived from D-fructose, and employed the coupling reaction with a dialkenylcupper reagent for the stereoselective formation of the *E*-olefin.[2b] Yoshikawa's group applied Darzens reaction followed by treatment with NaN_3 to a 1,3-dioxan-5-one derived from 2-deoxy-D-glucose for generation of the tetrasubstituted carbon, and they utilized Wittig reaction followed by *hν*-mediated isomerization with C_{14} phosphonium bromide to extend the side chain.[2c] Fujita and Nagao reported the synthesis of **1** in which Schöllkopf's bislactim method for construction of the tetrasubstituted carbon and Schlosser-type Wittig reaction to build the *E*-olefin were used.[2d] Synthesis of **1** by Hatakeyama's group employed the allenylmethylsilane chemistry and utilized intramolecular opening of a chiral epoxide by an imidate, assembling the carbon framework with a tetrasubstituted carbon stereoselectively.[2e] Pd-Catalyzed hydroxyamination of a vinyl epoxide[2f] and Darzens condensation[2g] were also employed for the stereoselective generation of the tetrasubstituted carbon in the formal synthesis of **1**. Recently, total synthesis of **2** has been reported from three laboratories. Trost developed Pd-catalyzed asymmetric alkylation of an azlactone to provide the key aldol-type intermediate bearing two stereogenic centers including the tetrasubstituted carbon, and succeeded in the stereoselective construction of *E*-olefin by Suzuki cross-coupling reaction, completing the asymmetric total synthesis of **2**.[4h] Lin's total synthesis of **2** from L-tartaric acid employed Baylis–Hillman reaction and Hatakeyama's method for a preparation of an oxazoline derivative possessing the tetrasubstituted carbon.[4i] Nakamura and Shiozaki reported the total synthesis of **2** from D-glucose, in which Darzens reaction and Suzuki coupling were involved as the key reactions.[4j] Synthesis and structure-activity relationship studies of myriocin[4c,8] and sphingofungins[4b] have also been carried out.

While several fascinating methods for construction of the tetrasubstituted carbon with nitrogen and efficient synthetic approaches toward natural α-substituted α-amino acids have been developed,[9] highly oxygenated structures of these natural products led us to explore a novel synthetic methodology, in which the rearrangement of allylic trichloroacetimidate (Overman rearrangement)[10,11] derived from aldohexoses is involved as the key transformation (Fig. 2). This methodology is supposed to be useful for the stereoselective synthesis of highly functionalized amino acid derivatives based on the following merits: (1) Overman rearrangement on furanose scaffolds is expected to show moderate to high stereoselectivities, since the chiral environment of sugars would control the facial selectivities of the rearrangement; and (2) the residual functionalities in carbohydrate could be utilized for the transformation of the rearranged product into highly functionalized acyclic or heterocyclic amino acid structures.[12] Based on this concept, we accomplished the total synthesis of lactacystin from D-glucose.[6d] In this paper we report another total synthesis[13] of natural products in this class [myriocin (**1**) and sphingofungin E (**2**)] from carbohydrates, which revealed the effectiveness of our novel methodology.

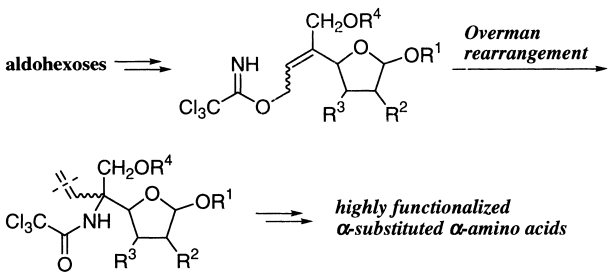


Fig. 2. Our methodology for a synthesis of α-substituted α-amino acids from aldohexofuranoses.

Results and Discussion

1. Total Synthesis of (+)-Myriocin from D-Mannose. Synthetic Plan. Myriocin (**1**) is a sphingosine-like compound consisting of a functionalized head, an unusual α-substituted serine framework with three contiguous chiral centers including a tetrasubstituted carbon with nitrogen, and a hydrophobic tail unit. Our retrosynthetic analysis, as mentioned above, suggested that the Overman rearrangement on furanose scaffolds, followed by further transformation utilizing the functional groups in the carbohydrate residue, would provide the highly functionalized intermediate for **1** in a stereoselective manner and short reaction steps. This idea involves disconnection of the carbon framework of **1** into allyl bromide **3** and the hydrophobic C_{12} counterpart, sulfone **4** (Fig. 3). The sulfone-allyl bromide coupling reaction, which had been employed in our previous total synthesis of sphingofungin D,[4e] a congener of sphingofungin E lacking a C-2 hydroxymethyl group, was expected to construct the carbon backbone possessing *E*-olefin in **1** stereoselectively. On the basis of these considerations, the functionalized part, allyl bromide **3** was planned to be prepared from furanose derivative **5** with the tetrasubstituted carbon. The furanose **5** would derive from Overman rearrange-

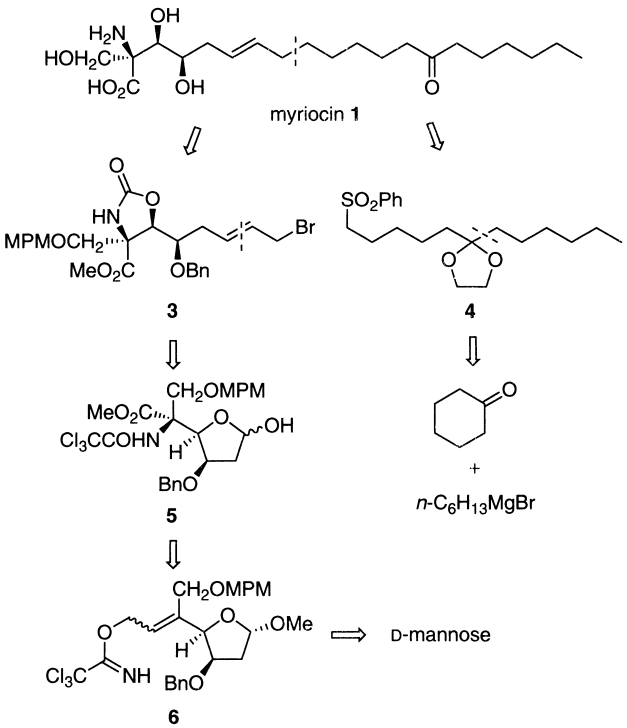
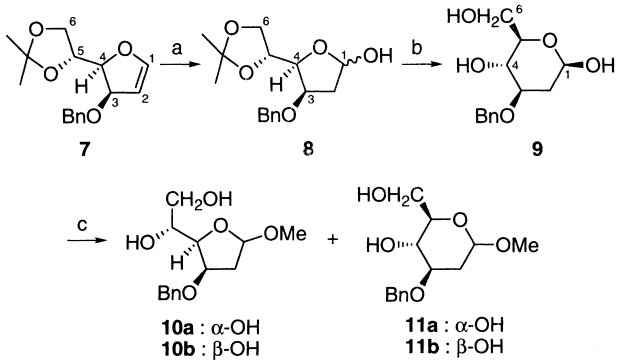


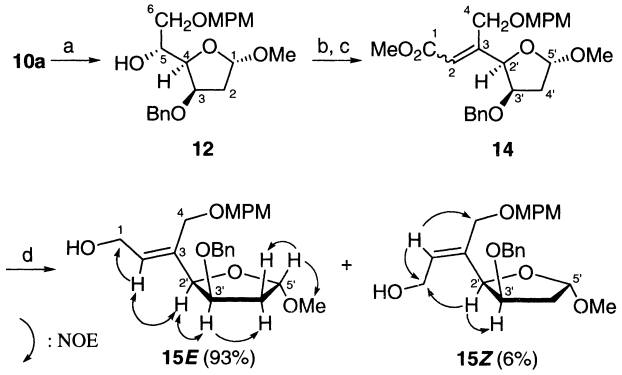
Fig. 3. Retrosynthetic analysis of myriocin (**1**).

ment of allylic trichloroacetimidate **6**, which was envisioned as arising from D-mannose. On the other hand, the sulfone **4**, the hydrophobic part of **1** was planned to be synthesized from cyclohexanone and C_6 Grignard reagent.

Functionalization of a Furanose Derivative. The known glycal **7**, prepared from D-mannose in 3 step reactions[14,15] [1) conc. H_2SO_4–acetone; 2) $(Me_2N)_3P$–CCl_4 then Li/NH_3–THF; 3) NaH–BnBr] in 70% overall yield, was converted into **8** by an oxymercuration-reduction sequence (Scheme 1). The acetonide group in **8** was removed by acid hydrolysis to give crystalline 3-*O*-benzyl-2-deoxy-β-D-glucose **9** in 91% yield from **7**. The coupling constant observed in **9** ($J_{1,2}$ = 9.8 Hz) revealed its anomeric configuration to be β. Treatment of **9** with acidic methanol at 0 °C gave a mixture of methyl furanosides **10a** and **10b**, and pyranosides **11a** and **11b** [**10a**: (mixture of **10b**, **11a**, and **11b**) = ca. 4:1, determined by ^{1}H NMR]. Fortunately, the major isomer, α-furanoside **10a** was obtained in pure form by direct recrystallization in 69% isolated yield. The mixture of undesired isomers could be again converted into a mixture of **10a**, **10b**, **11a** and **11b** via **9** by acid hydrolysis followed by methyl glycoside formation. The primary hydroxy group in **10a** was selectively protected by treatment with dibutyltin oxide[16] followed by benzylation to afford **12** in 96% yield (Scheme 2). Swern oxidation[17] of a hydroxy group in **12** gave **13**, and subsequent Horner–Wadsworth–Emmons type Wittig olefination[18] of **13** provided an inseparable mixture of α,β-unsaturated ester **14** (E:Z = ca. 15:1 ratio, determined by ^{1}H NMR) in 90% yield from **12**. When ketone **13** was subjected to the typical Wittig reaction conditions with stabilized ylide (Ph_3P=$CHCO_2Et$,[19] toluene, reflux), moderate Z-selectivity (E:Z = ca. 1:4 ratio, 78% yield) was observed.[20] DIBAL-H reduction of the ester **14**, followed by separation by silica gel column chromatography, gave **15*E*** and **15*Z*** in 93 and 6% isolated yields, respectively; their structures including geometries of the double bonds and anomeric configurations were confirmed by NOE experiments.



Scheme 1. Bn = –CH_2Ph. Reagents and conditions: a) Hg-$(OAc)_2$, THF–H_2O, then KI, $NaBH_4$, 0 °C; b) 60% AcOH aq, 91% from **7**; c) AcCl, MeOH, 0 °C; **10a** (69%).

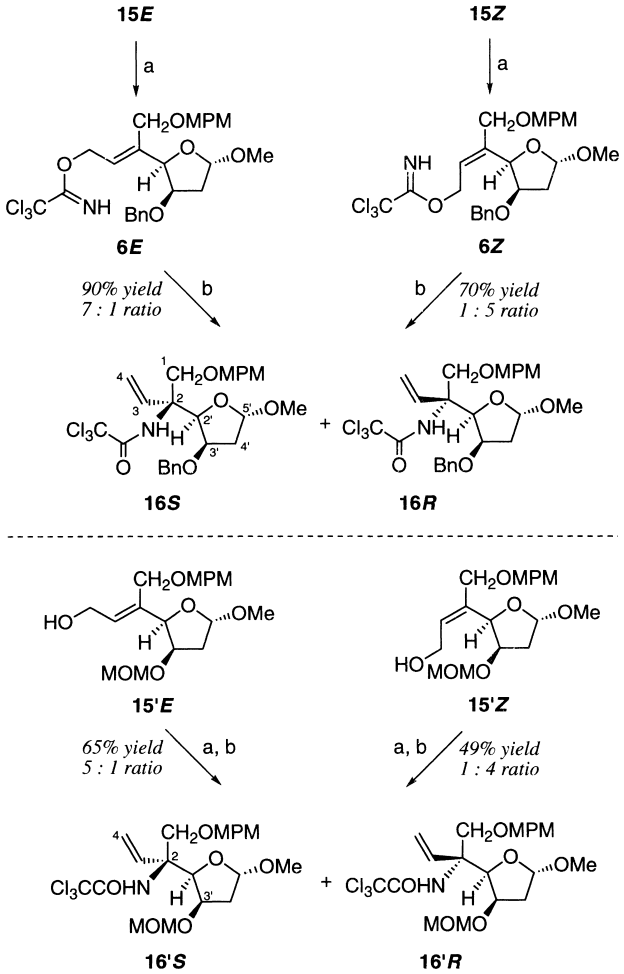


Scheme 2. MPM = –$CH_2C_6H_4$(*p*-OMe). Reagents and conditions: a) *n*-Bu_2SnO, toluene, reflux, then CsF, MPMCl, DMF, 80 °C, 96%; b) Swern oxidation, 100%; c) $(MeO)_2$-P(O)CH_2CO_2Me, LiBr, DBU, CH_3CN, −45 °C, 90%, E:Z = 15:1; d) DIBAL-H, toluene, −78 °C.

Overman Rearrangement. With the allylic alcohol **15*E*** in hand, we examined the crucial step, Overman rearrangement. Thus, an *o*-xylene solution of allylic trichloroacetimidate **6*E*** prepared from **15*E*** by the action of Cl_3CCN and DBU was heated at 140 °C in a sealed tube under argon in the presence of solid potassium carbonate[21] to afford the rearranged products **16*S*** and **16*R*** in 90% yield, as an inseparable mixture of diastereoisomers (**16*S***:**16*R*** = ca. 7:1 ratio, determined by ^{1}H NMR). Under similar conditions, the isomeric allylic alcohol **15*Z*** gave a 1:5 mixture of **16*S*** and **16*R*** in 70% yield (Scheme 3). Overman rearrangements of allyl alcohols **15′*E*** and **15′*Z***, possessing 3′-*O*-methoxymethyl ether (C-3 position of D-mannose) prepared from D-mannose by a procedure similar to that of 3′-*O*-benzyl ethers (**15*E*** and **15*Z***), were also carried out. The *E*-allyl alcohol **15′*E*** afforded **16′*S*** and **16′*R*** (4:1) in 65% yield, whereas its *Z*-isomer **15′*Z*** gave **16′*S*** and **16′*R*** (1:4) in 49% yield, respectively. These results suggest that the geometry of the carbon–carbon double bond in allylic trichloroacetimidates should be an important factor for the facial selectivity of the rearrangement, and that the ratio of the rearrangement is slightly influenced by the substituents on hydroxy group at the C-3 position of furanoses.

It has been reported that Overman rearrangement proceeds effectively in the presence of Pd(II) or Hg(II) catalysts at lower reaction temperature.[6b,d,j–m] However, attempted Pd(II)-catalyzed rearrangement of **6*E*** and **6*Z*** gave none of the rearranged product, but only led to the decomposition of the imidates. The failure of catalytic rearrangement of **6*E*** and **6*Z*** might be due to the steric factor; the bulky furan moiety with oxygen substituents would hinder the nucleophilic attack of imino-nitrogen to π-metal complex or/and the coordination of the catalyst to olefin. Furthermore, the Lewis acidity of Pd(II)[22] might induce the decomposition of the trichloroacetiminoyl group.

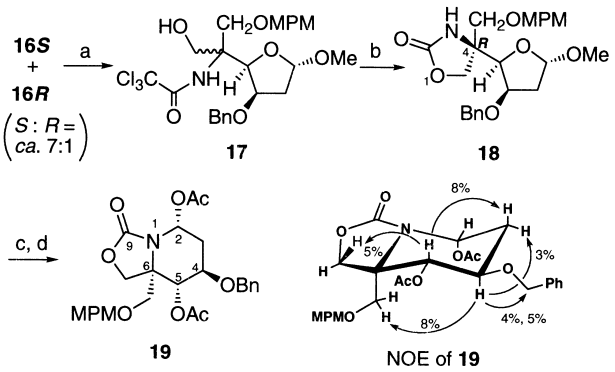
Preparation of Allyl Bromide. The stereochemistry of the newly generated tetrasubstituted carbon was confirmed by the following sequences. Ozonolysis of a mixture of the rearranged products **16*S*** and **16*R*** (ca. 7:1, prepared from **15*E***), followed by $NaBH_4$ reduction, afforded a primary alcohol **17**, whose treatment with base (DBU) caused intramolecular cyclization to give oxazolidinone **18** as the major product in 63% isolated yield after purification with silica gel chromatography (Scheme 4). Acid hydrolysis of **18** with 2 M HClaq–THF (1 M = 1 mol dm^{-3}) followed by acetylation gave bicyclic aminal derivative **19**. NOE experiments of acetate **19** showed that the tetrasubstituted carbon in **19** possessed 6*R* configuration, revealing that the major stereoisomer of the rearrangement (**16*S***) should be 2*S*-isomer.



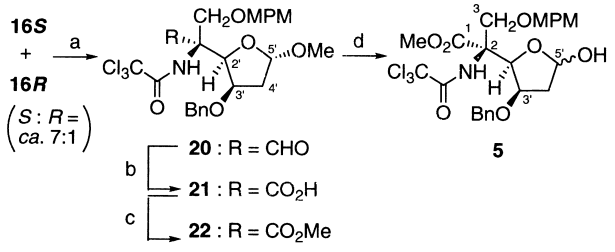
Scheme 3. MOM = –CH_2OMe. Reagents and conditions: a) Cl_3CCN, DBU, CH_2Cl_2, 0 °C; b) xylene, K_2CO_3, 140 °C, in a sealed tube.

The stereochemical assignment has shown that the transformation of the vinyl function in **16*S*** into carboxylic acid moiety is required for the synthesis of **1**. Although Lemieux–Johnson oxidation[23] of the mixture of **16*S*** and **16*R*** (ca. 7:1, prepared from **15*E***) required long reaction time for completion and resulted in a low yields of the desired products, ozonolysis of the mixture (Me_2S workup), followed by chromatographic separation, successfully provided (*S*)-aldehyde **20** and its (*R*)-isomer in 81 and 12% isolated yields, respectively (Scheme 5). Further oxidation of **20** with $NaClO_2$ and subsequent esterification (Me_3SiCHN_2)[24] afforded methyl ester **22** in 98% yield. Acidic hydrolysis of **22** provided lactol **5**, possessing the correct stereochemistries and proper functionalities for the introduction of the side chain, in 76% yield.

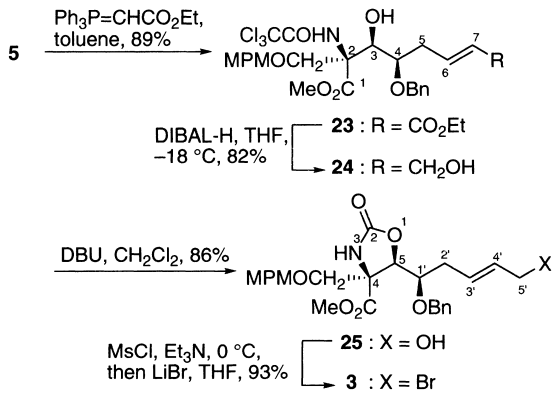
Wittig reaction of the lactol **5** with stabilized ylide ($Ph_3P{=}CHCO_2Et$, toluene, 25 °C) successfully afforded (*E*)-α,β-unsaturated ester **23** exclusively in 89% yield (Scheme 6). When compound **23** was treated with DIBAL-H (in THF, −18 °C), only α,β-unsaturated ester function was reduced to give allylic alcohol **24** in 82% yield. The observed coupling constant in **24** ($J_{6,7}$ = 15.4 Hz) clearly supported the (*E*)-geometry of the double bond. Reaction with DIBAL-H in other solvents (CH_2Cl_2 or toluene) or higher reaction temperature reduced the methoxycarbonyl as well as *N*-trichloroacetamide functions to give significant amounts of more polar, undesired products. In order to prepare allyl bromide suitable for the coupling reaction, protection of the secondary hydroxy group in **24** was investigated. Since attempted protection by ether formation (Bn, MPM, MOM, TBS, TES and TMS) gave no satisfactory results, we selected the cyclic carbamate as the protecting group for both hydroxy and amino functions. Thus, treatment of **24** with DBU smoothly induced cyclization to afford oxazolidinone **25** in 86% yield. Although reaction of **25** with CBr_4 and Ph_3P gave many unidentified products, it was found that *O*-mesylation followed by treatment with LiBr[25] showed good results, and the desired **3** was obtained in 93%



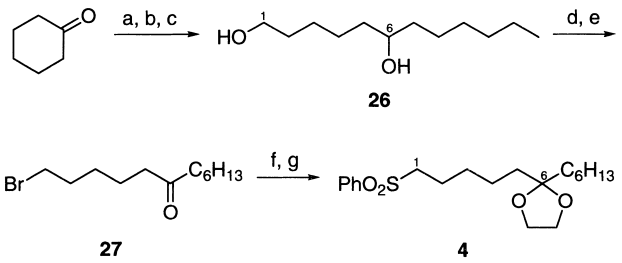
Scheme 4. Reagents and conditions: a) O_3, MeOH, −78 °C, then $NaBH_4$, 0 °C; b) DBU, CH_2Cl_2, 63% for 2 steps; c) 2 M HCl aq–THF (1:1); d) Ac_2O, pyridine, 90% for 2 steps.



Scheme 5. Reagents and conditions: a) O_3, CH_2Cl_2, −78 °C, then Me_2S, 0 °C, 81%; b) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, $HOSO_2NH_2$, *t*-BuOH–H_2O; c) Me_3SiCHN_2, MeOH, 98% for 2 steps; d) 4 M HCl aq–THF (1:3), 76%.



Scheme 6.



Scheme 7. Reagents and conditions: a) n-$C_6H_{13}MgBr$, Et_2O; b) I_2, o-xylene, reflux; c) O_3, MeOH, 0 °C then $NaBH_4$, 53% for 3 steps; d) CBr_4, Ph_3P, CH_2Cl_2, −15 °C; e) Jones oxidation; f) $PhSO_2Na{\cdot}2H_2O$, DMF; g) $(TMSOCH_2)_2$, TMSOTf, CH_2Cl_2, 71% from **26**.

yield from **25**.

Coupling Reaction and Completion of the Total Synthesis. A hydrophobic part of myriocin, the C_{12} side chain possessing a sulfone and a masked carbonyl group, was synthesized from cyclohexanone (Scheme 7). The known diol **26**,[26] prepared from cyclohexanone in 3-step reactions by essentially the same procedure as that reported by Payette and Just,[2e] was converted into primary bromide, whose oxidation gave bromo ketone **27**. Treatment of **27** with $PhSO_2Na$, followed by ketalization[27] gave **4** in 71% yield from **26**.

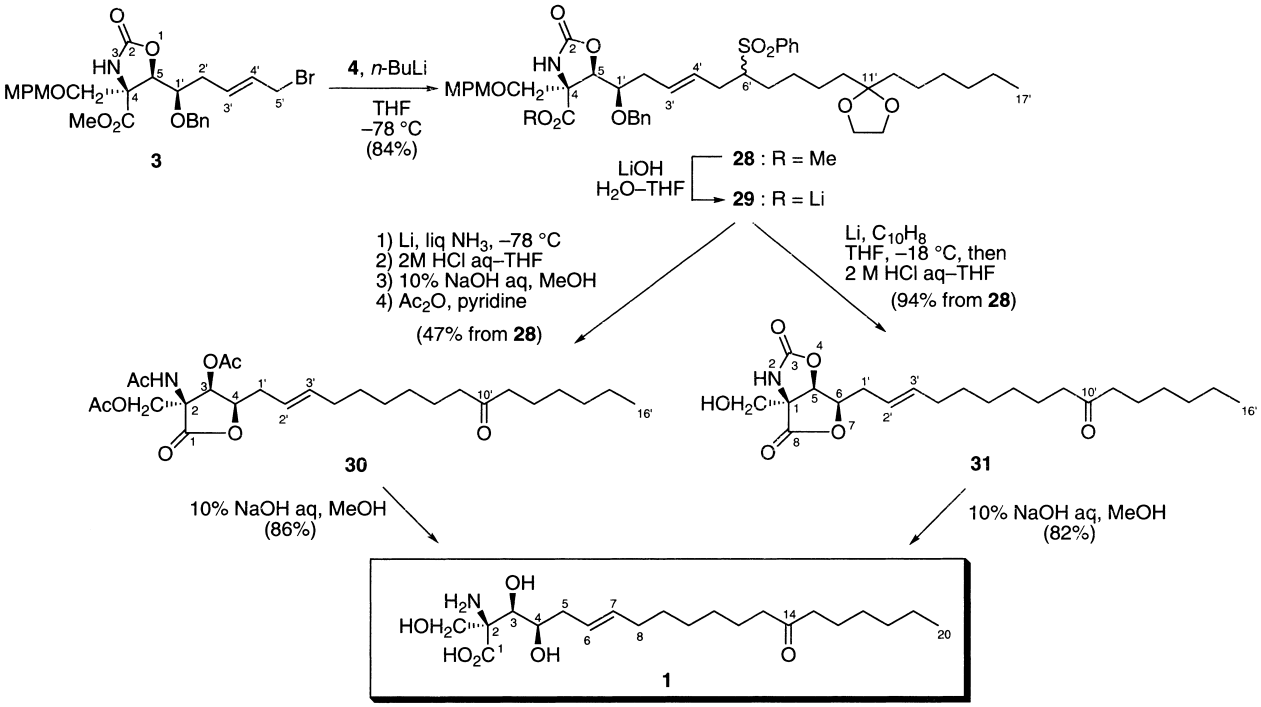
Sulfone **4** was lithiated with n-BuLi in THF at −78 °C, and then reacted with the allyl bromide **3** to give coupling product **28** as a mixture of diastereomers in 84% yield (Scheme 8). Saponification of **28** and subsequent Birch reduction (Li, liquid NH_3) successfully removed sulfonyl, O-benzyl and O-(p-methoxybenzyl) groups. Deprotections of the ketal group by acid hydrolysis and of the carbamate function by alkaline hydrolysis, followed by conventional acetylation, provided the known γ-lactone **30**[2d] in 47% overall yield from **28**. The spectral and physical data for **30** were identical in all respects to those provided by Professor Hatakeyama. Saponification[2d] followed by neutralization with IRC-76 resin (H^+ form) furnished (+)-myriocin **1** in 86% yield. The spectral (^1H and ^{13}C NMR) data for synthetic **1** were fully identical with those of natural myriocin, and the physical properties of **1** showed good agreement {168.4–170.1 °C, $[\alpha]_D^{25}$ +5.1 (c 0.175, MeOH); lit.[1c] 169–171 °C, $[\alpha]_D$ +4.8 (c 0.286, MeOH)} with those reported for the natural product. Therefore, total synthesis of myriocin has been accomplished. However, the relatively low yields and longer reaction sequences in conversion of **28** to **1** via **30** (6 steps in 40% overall yield) led us to search for more effective synthetic pathways. After several attempts, it was found that use of Li–naphthalene[28] gave excellent results. Thus, treatment of **29** with Li–naphthalene in THF at −18 °C, followed by acidic treatment, gave bicyclic γ-lactone **31** in 94% yield from **28**. Saponification of **31** with 10% aqueous NaOH–MeOH and subsequent neutralization with resin furnished **1** in 82% yield.

2. Total Synthesis of (−)-Sphingofungin E from D-Glucose. Synthetic Plan. Sphingofungin E (**2**) has four consecutive chiral centers including α-substituted α-amino acid moiety. Recent successful total syntheses of **2**[4h–j] revealed that it is a (5R)-hydroxy derivative of myriocin. The structural resemblance of **2** and **1** suggested that the methodology employed for the total synthesis of **1** would be applicable to the synthesis of **2**; thus Overman rearrangement of an imidate derived from D-glucofuranose was expected to provide the proper intermediate with correct stereochemistries for the synthesis of **2**.

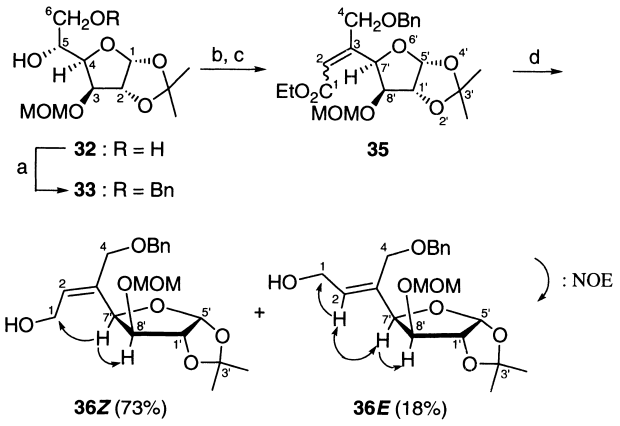
Overman Rearrangement of a Functionalized Furanose. The known diol **32**,[29] prepared from D-glucose in 3-step reactions [1) conc. H_2SO_4–acetone; 2) MOMCl–iPr$_2$NEt; 3) AcOH aq], was heated with dibutyltin oxide in toluene under reflux, and then treated with BnBr–CsF in DMF to give **33** in 88% yield (Scheme 9). Swern oxidation gave ketone **34**, which was then reacted with stabilized ylide ($Ph_3P{=}CHCO_2Et$) to afford an inseparable mixture of unsaturated ester **35** (E:Z = 1:4 ratio) in 98% for 2 steps. DIBAL-H reduction of the ester function and subsequent chromatographic separation gave Z-allylic alcohol **36*Z*** (73%) and its E-isomer **36*E*** (18%). The NOE experiments of **36*Z*** and **36*E*** clearly assigned their structures.

Overman rearrangement of allylic trichloroacetimidates derived from **36*Z*** and **36*E*** was found to show stereoselectivities similar to those observed in the reactions of **15*Z*** and **15*E***. Treatment of **36*Z*** with Cl_3CCN and DBU generated trichloroacetimidate, whose thermal rearrangement (140 °C in o-xylene in the presence of K_2CO_3 under Ar) afforded **37*R*** and its (2S)-isomer **37*S*** in 64 and 14% isolated yields from **36*Z***, respectively (Scheme 10). Similar treatment of **36*E*** gave **37*R*** and **37*S*** in 12 and 45% isolated yields. Ozonolysis of **37*R*** followed by Me_2S treatment afforded the corresponding aldehyde. Reduction of the aldehyde by $Zn(BH_4)_2$[30] provided alcohol **38** in 93% yield from **37*R***. It was required to use $Zn(BH_4)_2$ for the reduction of the aldehyde, because $NaBH_4$ or $NaBH_3CN$[31] reduction was found to be less satisfactory; $NaBH_4$ induced the partial formation of a carbamate, and $NaBH_3CN$ cleaved the methoxymethyl and/or acetonide groups to give a complex mixture. The newly constructed stereochemistry in the rearranged product **37*R*** was confirmed by conversion of **37*R*** into its bicyclic derivative **39**. Thus, base treatment followed by acid hydrolysis and acetylation afforded bicyclic aminal **39** in 38% overall yield, whose single crystal X-ray analysis[32] clearly showed that the major isomer of the rearrangement product **37*R*** has (2R)-configuration. Therefore, it is now clear that the primary alcohol originating from D-glucose should be transformed into a carboxylic acid moiety, and the newly generated alcohol in **38** should correspond to the primary alcohol moiety of sphingofungin E.

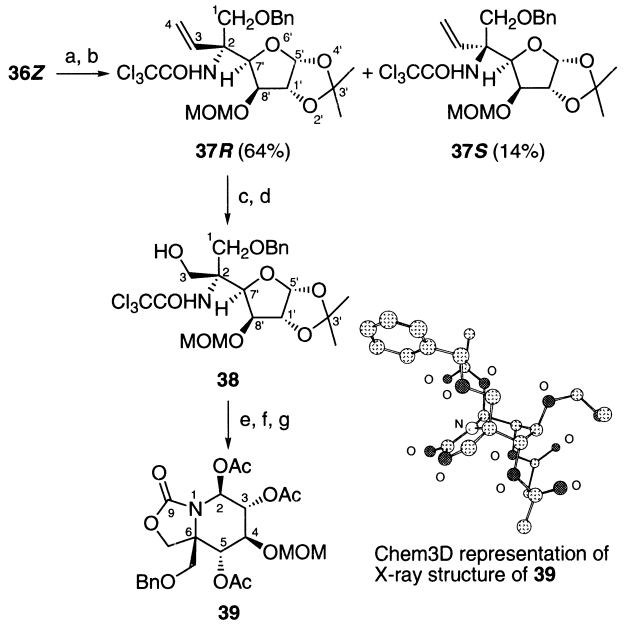
Coupling Reaction and the Total Synthesis. Acid hydrolysis of **38** removed methoxymethyl and acetonide protecting groups to give furanose **40**, which is then treated with the stabilized ylide ($Ph_3P{=}CHCO_2Et$) to afford (E)-α,β-unsaturated ester **41** exclusively (Scheme 11). The resulting tetrol **41** was treated with $(MeO)_2CMe_2$–CSA to afford diacetonide **42** in 46% yield from **38**. Treatment of **42** with DIBAL-H at −78 °C, in contrast with the results of **23**, reduced the ester function as well as the N-trichloroacetamide moiety to afford an amine, which was isolated as its N-Boc derivative **43** in 90% yield. The allylic alcohol was converted into bromide to give the highly functionalized part **44** of sphingofungin E in 90% yield. Coupling reaction of the allyl bromide **44** with the side chain **4**, under conditions similar to those employed for the coupling of **3** with **4**, successfully afforded the carbon



Scheme 8.



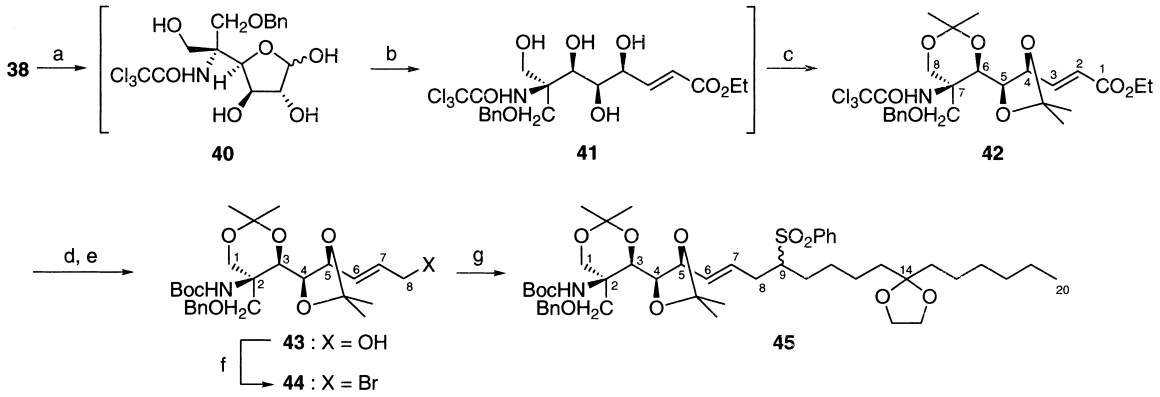
Scheme 9. Reagents and conditions: a) n-Bu_2SnO, toluene, reflux, then CsF, BnBr, DMF, 50 °C, 88%; b) Swern oxidation; c) $Ph_3P{=}CHCO_2Et$, toluene, 100 °C, 98% for 2 steps, $E{:}Z$ = 1:4; d) DIBAL-H, toluene, −78 °C.



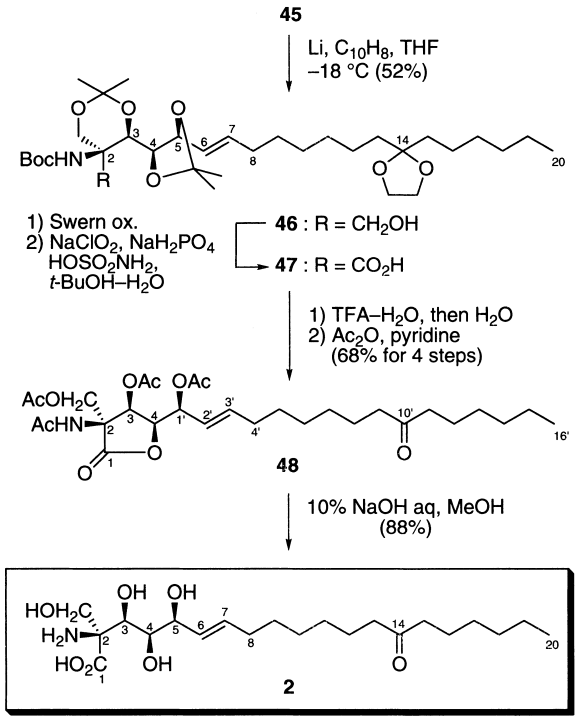
Scheme 10. Reagents and conditions: a) Cl_3CCN, DBU, CH_2Cl_2, 0 °C; b) xylene, 140 °C, in a sealed tube, K_2CO_3; c) O_3, CH_2Cl_2, −78 °C then Me_2S, 0 °C; d) $Zn(BH_4)_2$, Et_2O, 0 °C, 91%; e) DBU, CH_2Cl_2, 0 °C; f) TFA–H_2O (1:1), 0 °C; g) Ac_2O, pyridine, 48% for 3 steps.

framework of sphingofungin E **45** in 85% yield as a mixture of diastereomers.

Treatment of **45** with Li and naphthalene in THF removed both sulfonyl and *O*-benzyl groups to give primary alcohol **46** in 52% yield (Scheme 12). Swern oxidation followed by $NaClO_2$ treatment provided the protected amino acid **47**. All protecting groups in **47**: two acetonides, an ethyleneketal and a *tert*-butoxycarbonyl, were removed by acid hydrolysis (TFA–THF–H_2O) to afford a mixture of sphingofungin E (**2**) and its γ-lactone. Since the separation of them was found to be difficult at this stage, the mixture was treated with Ac_2O and pyridine to give tetraacetylated γ-lactone **48** in 68% yield from **46**. Finally, (−)-**2** was obtained in 88% yield by saponification of **48**, followed by neutralization with Amberlite IRC-76. The physical properties of synthetic **2** {144.0–145.8 °C, $[\alpha]_D^{25}$ −5.6 (c 0.14, MeOH); lit.[4i] 145–147 °C, $[\alpha]_D$ −5.43 (c 0.48, MeOH)} as well as spectroscopic data (^1H and ^{13}C NMR) showed good accordance with those reported for the authentic sample.[4i]



Scheme 11. Reagents and conditions: a) 12 M HCl aq–THF (1:2); b) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2; c) $Me_2C(OMe)_2$, CSA, 46% from **38**; d) DIBAL-H, toluene, −78 °C; e) Boc_2O, $NaHCO_3$, MeOH, 90% for 2 steps; f) MsCl, Et_3N, CH_2Cl_2 then LiBr, THF, 90%; g) **4**, *n*-BuLi, THF, −78 °C, 85%.



Scheme 12.

Conclusion

Total synthesis of myriocin (**1**) from D-mannose and sphingofungin E (**2**) from D-glucose was accomplished. This work established a novel synthetic pathway to myriocin, sphingofungins, and their derivatives. In these studies, two intriguing experimental facts were revealed: (1) Overman rearrangement of allylic trichloroacetimidates derived from furanose derivatives proceeded in high yields with moderate stereoselectivities, and the facial selection of the rearrangement was found to depend mainly on the geometry of the carbon–carbon double bonds in the allylic imidates; and (2) both stereoisomers of the rearranged products could be converted into the amino acid structure possessing *the same* configuration by reductive or oxidative transformation of a formyl function derived from a vinyl group, generated by the rearrangement. These results suggested that our synthetic protocol is applicable to the stereoselective synthesis for either (*R*)- or (*S*)-α-substituted α-amino acid structures. This work and previous success in total synthesis of lactacystin[6d] also revealed that the methodology involving Overman rearrangement on furanose scaffolds, followed by further manipulation by use of the residual functional groups in carbohydrates, is quite effective for the chiral synthesis of natural products possessing complex α-substituted α-amino acid structures.

Experimental

General. Melting points were determined on a Mitamura-Riken micro hot stage and were not corrected. Optical rotations were recorded using a sodium lamp (589 nm) with a JASCO DIP-370 instrument with 1 dm tube. Infrared (IR) spectra were measured with a JASCO FT/IR-200 spectrometer and were reported in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded at 300 MHz on a JEOL *Lambda* 300 or on a Varian MVX-300 spectrometer. Chemical shifts are reported as δ values in ppm relative to tetramethylsilane ($\delta = 0$) or chloroform ($\delta = 7.26$). Coupling constants (J) are reported in Hz. Abbreviations used are: b (broad peak), s (singlet), d (doublet), t (triplet), q (quartet) and m (complex multiplet). ^{13}C NMR spectra were recorded at 75 MHz on a JEOL *Lambda* 300 spectrometer. Chemical shifts are reported as δ values in ppm relative to chloroform-*d* ($\delta = 77.00$) or methanol-d_4 ($\delta = 49.00$) as internal references. Mass spectra are measured by a JEOL GC Mate spectrometer with EI (70 eV) or FAB mode. Organic extracts were dried over solid anhydrous Na_2SO_4 and concentrated below 40 °C under reduced pressure. Column chromatography was carried out with silica gel (Merck Kieselgel 60 F_{254}; 230–400 mesh) or alumina powder (WAKO alumina, activated; 300 mesh) for purification. Preparative TLC (PLC) was performed with Merck PLC plate (Kieselgel 60 F_{254}, 0.5 mm thickness).

1,4-Anhydro-3-*O*-benzyl-5,6-*O*-isopropylidene-D-*arabino*-hex-1-enitol (7).[15] To a solution of diacetone-D-mannose[14] (10.0 g, 38.4 mmol) in THF (160 mL) were added CCl_4 (5.56 mL, 57.6 mmol) and $(Me_2N)_3P$ (7.68 mL, 42.3 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, then warmed up to 0 °C and stirred at 0 °C for 5 more min. The resulting yellow solution of glycosyl chloride was added into a navy blue suspension

of Li (5.33 g, 0.768 mol) in freshly distilled liquid ammonia (200 mL, from Li) at −78 °C. After the reaction mixture had been stirred at −78 °C for 30 min, solid NH_4Cl (61.6 g, 1.17 mol) was added portionwise to it at −78 °C. The resulting suspension was stirred at −40 °C until the blue color of the mixture disappeared. Then the mixture was stirred at 0 °C for 1 h to evaporate the remaining ammonia. To the resulting gray suspension H_2O was added carefully, and the products were extracted with $CHCl_3$ and then dried. Removal of the solvent gave a residue, which was passed through a short column (100 g silica gel, 1:2 EtOAc–hexane containing 1 vol% Et_3N as an eluent) to afford crude glycal (6.77 g) as a pale yellow oil, which was used for the next reaction without further purification: $R_f = 0.43$ (1:1 EtOAc–toluene).

At 0 °C, a THF (100 mL) solution of the crude glycal (6.77 g) was added dropwise to a suspension of NaH (2.91 g, 72.7 mmol, washed with hexane) in THF (35 mL). Then the mixture was stirred at 0 °C for 15 min. To this suspension were added BnBr (9.51 mL, 80.0 mmol) and *n*-Bu_4NI (671 mg, 1.82 mmol) at 0 °C. After the reaction mixture had been stirred at 25 °C for 2 h, H_2O at 0 °C was added to it until the mixture became homogenous. The products were extracted with EtOAc and the organic layer was washed successively with 20% aqueous $Na_2S_2O_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was passed through a short column (100 g silica gel, 1:5 EtOAc–hexane containing 1 vol% Et_3N as an eluent) to afford glycal benzyl ether **7** (9.74 g, 97%) as a pale yellow syrup: $R_f = 0.67$ (1:2 EtOAc–hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.48 (s, 3H), 3.99 (dd, 1H, J = 6.6 and 8.4 Hz), 4.11 (dd, 1H, J = 6.6 and 8.4 Hz), 4.44 (dd, 1H, J = 5.1 and 7.0 Hz), 4.51 (d, 1H, J = 11.8 Hz), 4.58 (d, 1H, J = 11.8 Hz), 4.59 (dd, 1H, J = 5.1 and 6.6 Hz), 4.66 (dd, 1H, J = 2.7 and 7.0 Hz), 5.29 (dd, 1H, J = 2.7 and 2.7 Hz), 6.62 (d, 1H, J = 2.7 Hz), 7.28–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 26.6, 66.1, 71.1, 73.2, 79.4, 84.3, 102.0, 108.8, 127.6, 127.7, 128.5, 138.6, 150.7. The spectral data were identical with those reported.[14c]

3-*O*-Benzyl-2-deoxy-β-D-*arabino*-hexopyranose (9). To a mixture of glycal **7** (5.85 g, 21.2 mmol) in THF–H_2O (1:1, 120 mL) was added $Hg(OAc)_2$ (7.42 g, 23.3 mmol) at 25 °C. After this mixture had been stirred at 25 °C for 30 min, the resulting clear solution was cooled to 0 °C. To this solution was added an aqueous solution of KI (17.5 g, 0.105 mol in 20 mL water) and the resulting mixture was stirred at 0 °C for 15 min. To this reaction mixture was added an aqueous solution of $NaBH_4$ (801 mg, 21.2 mmol in 50 mL H_2O) dropwise over 1 h at 0 °C, and the resulting suspension was stirred vigorously at 0 °C for 30 min. The insoluble material was removed by filtration through a pad of Celite; this Celite was rinsed with EtOAc (100 mL × 3). The filtrate was separated and the organic layer was washed successively with saturated aqueous KI solution, saturated aqueous $Na_2S_2O_3$ solution and brine, and then dried. Removal of the solvent afforded furanose **8** (6.33 g) as a pale yellow syrup, which was used for the next reaction without further purification: $R_f = 0.19$ (1:2 EtOAc–hexane).

A solution of crude **8** (6.33 g) in 60% aqueous AcOH solution (130 mL) was stirred at 25 °C for 14 h. The resulting mixture was concentrated to give a residue, which was recrystallized from EtOH–petroleum ether (1:9, 200 mL) to afford hexose **9** (4.89 g, 91%) as white crystals. R_f = 0.1 (3:1 EtOAc–hexane); Mp 119.8–123.6 °C; $[\alpha]_D^{23.5}$ +25.4 (*c* 0.86, CH_3OH, after 3 h at 25 °C); IR (KBr) 1360, 1400, 1455, 1495, 2900, 2940, 3230 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 1.46 (ddd, 1H, J = 9.8, 11.6 and 12.4 Hz), 2.33 (ddd, 1H, J = 2.0, 4.9 and 12.4 Hz), 3.29 (ddd, 1H, J = 2.3, 5.7 and 9.5 Hz), 3.39 (bdd, 1H, J = 9.5 and 9.5 Hz), 3.53 (ddd, 1H, J = 4.9, 9.5 and 11.6 Hz), 3.73 (dd, 1H, J = 5.7 and 11.7 Hz), 3.91 (dd, 1H, J = 2.3 and 11.7 Hz), 4.71 (s, 2H), 4.79 (dd, 1H, J = 2.0 and 9.8 Hz), 7.30–7.45 (m, 5H); ^{13}C NMR (75 MHz, CD_3OD) δ 39.3, 63.0, 71.9, 72.7, 78.0, 80.3, 95.1, 128.6, 128.9, 129.3, 140.1; EI-MS *m/z* 254 (M^+, 5.2%), 236 (3.3), 163 (10.6), 86 (100); EI-HRMS Calcd for $C_{13}H_{18}O_5$ (M^+): 254.1154, Found: *m/z* 254.1142. Found: C, 61.20; H, 7.20%. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14%.

Methyl 3-*O*-Benzyl-2-deoxy-α-D-*arabino*-hexofuranoside (10a). To a solution of AcCl (0.0617 mL) in MeOH (40 mL) was added hexose **9** (2.00 g, 7.87 mmol) at 0 °C. After being stirred at 0 °C for 20 h, the reaction mixture was neutralized with Et_3N, and concentrated to give a solid residue, which was recrystallized from EtOAc–hexane (3:4, 21 mL) to afford methyl furanoside **10a** (1.46 g, 69%) as white crystals: $R_f = 0.46$ (6:1 EtOAc–hexane); Mp 93.2–95.4 °C; $[\alpha]_D^{24.0}$ +31.9 (*c* 0.62, $CHCl_3$); IR (KBr) 1035, 1050, 2940, 3230 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (ddd, 1H, J = 2.4, 6.1 and 13.7 Hz), 2.20 (ddd, 1H, J = 5.1, 5.1 and 13.7 Hz), 1.63–2.24 (m, 1H), 3.08 (bs, 1H), 3.31 (s, 3H), 3.64–3.71 (m, 1H), 3.76–3.84 (m, 1H), 3.95–4.00 (m, 2H), 4.38 (d, 1H, J = 11.6 Hz), 4.39 (m, 1H), 4.59 (d, 1H, J = 11.6 Hz), 5.11 (dd, 1H, J = 2.4 and 5.1 Hz), 7.27–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.8, 55.1, 64.6, 70.5, 71.5, 78.8, 78.9, 104.1, 127.7, 128.1, 128.7, 137.2; EI-MS *m/z* 268 (M^+, 6.2%), 236 (17.1), 177 (97.8), 99 (100); EI-HRMS Calcd for $C_{14}H_{20}O_5$ (M^+): 268.1311, Found: *m/z* 268.1309. Found: C, 62.84; H, 7.59%. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51%.

Methyl 3-*O*-Benzyl-6-*O*-(4-methoxybenzyl)-2-deoxy-α-D-*arabino*-hexofuranoside (12). To a solution of diol **10a** (1.22 g, 4.55 mmol) in toluene (25 mL) was added dibutyltin oxide (1.13 g, 4.55 mmol) and the mixture was stirred under reflux for 2 h. The resulting mixture was concentrated to give a residue, which was dissolved in DMF (40 mL) at 40 °C. To this suspension were added CsF (0.83 g, 5.46 mmol) and *p*-methoxybenzyl chloride (0.74 mL, 5.46 mmol) at 40 °C and the mixture was stirred at 80 °C for 40 h. After cooling, to the reaction mixture were added 20% aqueous KF solution (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL). The resulting mixture was stirred for 2 h at 25 °C, and then extracted with EtOAc. The organic layer was washed successively with H_2O, 20% aqueous KF solution, and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (50 g silica gel, 1:4 EtOAc–hexane as an eluent) to afford *p*-methoxybenzyl ether **12** (1.70 g, 96%) as a pale yellow syrup: $R_f = 0.73$ (3:1 EtOAc–hexane); $[\alpha]_D^{23.5}$ +25.8 (*c* 0.85, $CHCl_3$); IR (neat) 1040, 1105, 1250, 1515, 1615, 2930, 3480 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (ddd, 1H, J = 2.7, 6.1 and 14.1 Hz), 2.26 (ddd, 1H, J = 2.7, 5.6 and 14.1 Hz), 3.03 (d, 1H, J = 5.3 Hz), 3.33 (s, 3H), 3.60 (dd, 1H, J = 5.9 and 9.9 Hz), 3.71 (dd, 1H, J = 3.7 and 9.9 Hz), 3.80 (s, 3H), 3.99 (dd, 1H, J = 4.4 and 7.6 Hz), 4.16 (m, 1H), 4.32 (m, 1H), 4.41 (d, 1H, J = 11.7 Hz), 4.50 (s, 2H), 4.56 (d, 1H, J = 11.7 Hz), 5.14 (dd, 1H, J = 2.7 and 5.6 Hz), 6.87 (d, 2H, J = 8.3 Hz), 7.25–7.35 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.3, 55.2, 55.3, 69.1, 71.5, 71.7, 73.1, 78.9, 79.0, 104.2, 113.8, 127.7, 127.9, 128.5, 129.4, 130.3, 137.5, 159.2; EI-MS *m/z* 388 (M^+, 2.1%), 356 (31.7), 121 (100); EI-HRMS Calcd for $C_{22}H_{28}O_6$ (M^+): 388.1886, Found: *m/z* 388.1884. Found: C, 67.99; H, 7.31%. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27%.

Methyl 3-*O*-Benzyl-6-*O*-(4-methoxybenzyl)-2-deoxy-α-D-*threo*-hexofuranos-5-uloside (13). A mixture of $(COCl)_2$ (2.0

M solution in CH_2Cl_2, 10.9 mL, 21.8 mmol) and DMSO (3.10 mL, 43.7 mmol) was stirred at −78 °C for 30 min. To the stirred mixture was added a solution of alcohol **12** (1.70 g, 4.37 mmol) in CH_2Cl_2 (23 mL). After the reaction mixture had been stirred at −78 °C for 2.5 h, Et_3N (9.13 mL, 65.5 mmol) was added , and the resulting suspension was stirred at 0 °C for more 30 min. This mixture was poured into saturated aqueous NH_4Cl solution, and the products were extracted with EtOAc. The organic layer was washed with brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (32 g silica gel, 1:3 EtOAc–hexane as an eluent) to afford ketone **13** (1.68 g, 100%) as a colorless syrup: R_f = 0.48 (1:1 EtOAc–hexane); $[\alpha]_D^{26.5}$ +14.0 (*c* 1.34, $CHCl_3$); IR (neat) 1035, 1060, 1115, 1250, 1515, 1615, 1730, 2840, 2910, 2935 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.09 (ddd, 1H, *J* = 2.7, 6.1 and 14.1 Hz), 2.29 (ddd, 1H, *J* = 2.7, 5.4 and 14.1 Hz), 3.38 (s, 3H), 3.81 (s, 3H), 4.31 (d, 1H, *J* = 17.0 Hz), 4.37 (d, 1H, *J* = 17.0 Hz), 4.38 (d, 1H, *J* = 11.8 Hz), 4.42 (d, 1H, *J* = 11.8 Hz), 4.49 (d, 1H, *J* = 11.8 Hz), 4.50 (d, 1H, *J* = 11.8 Hz), 4.55–4.59 (m, 1H), 4.70 (d, 1H, *J* = 5.1 Hz), 5.29 (dd, 1H, *J* = 2.7 and 5.4 Hz), 6.59 (d, 2H, *J* = 8.5 Hz), 7.21–7.37 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.1, 55.2, 55.5, 71.6, 72.8, 74.1, 79.8, 84.1, 105.2, 113.7, 127.7, 127.8, 128.4, 129.4, 129.5, 137.3, 159.3, 204.9; EI-MS *m/z* 386 (M^+, 0.2%), 295 (0.4), 121 (76.0), 91 (100); EI-HRMS Calcd for $C_{22}H_{26}O_6$ (M^+): 386.1729, Found: *m/z* 386.1732.

An Inseparable Mixture of Methyl (*E*)-3-[(2*R*,3*R*,5*S*)-3-Benzyloxy-5-methoxyoxolan-2-yl]-4-(4-methoxybenzyloxy)-but-2-enoate and Its (*Z*)-Isomer (14). To a mixture of LiBr (0.76 g, 8.73 mmol, dried at 140 °C under reduced pressure just before use) in CH_3CN (10 mL) were added methyl dimethoxyphosphinoylacetate (1.41 mL, 8.73 mmol) and DBU (1.31 mL, 8.73 mmol) at 25 °C. The mixture was stirred at −45 °C for 15 min. To the resulting colorless solution was added a solution of ketone **13** (1.68 g) in CH_3CN (10 mL) at −45 °C. After this mixture had been stirred for 12 h at −45 °C, the resulting suspension was diluted with EtOAc and washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (120 g silica gel, 1:6 EtOAc–hexane as an eluent) to afford a mixture (*E*:*Z* = ca. 15:1) of unsaturated ester **14** (1.74 g, 90%) as a colorless syrup: R_f = 0.52 (1:2 EtOAc–hexane); IR (neat) 1055, 1110, 1150, 1215, 1250, 1515, 1585, 1615, 1650, 1715, 2840, 2950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, for the major isomer) δ 2.08 (ddd, 1H, *J* = 2.9, 6.1 and 14.1 Hz), 2.28 (ddd, 1H, *J* = 2.1, 5.6 and 14.1 Hz), 3.36 (s, 3H), 3.70 (s, 3H), 3.79 (s, 3H), 4.26 (d, 1H, *J* = 11.9 Hz), 4.28 (d, 1H, *J* = 11.2 Hz), 4.32–4.36 (m, 1H), 4.38 (d, 1H, *J* = 11.2 Hz), 4.41 (d, 1H, *J* = 11.9 Hz), 4.46 (bd, 1H, *J* = 14.9 Hz), 4.90 (bd, 1H, *J* = 3.4 Hz), 4.96 (bd, 1H, *J* = 14.9 Hz), 5.21 (dd, 1H, *J* = 2.9 and 5.6 Hz), 6.22 (m, 1H), 6.84 (d, 2H, *J* = 8.6 Hz), 7.15–7.32 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.1, 51.3, 55.4, 55.5, 68.4, 71.4, 72.9, 79.2, 79.9, 103.9, 113.9, 115.5, 127.8, 127.9, 128.5, 129.6, 130.3, 138.1, 154.8, 159.4, 166.9; EI-MS *m/z* 442 (M^+, 0.1%), 410 (0.1), 351 (0.2), 274 (21.3), 91 (100); EI-HRMS Calcd for $C_{25}H_{30}O_7$ (M^+): 442.1992, Found: *m/z* 442.1995. Found: C, 67.69; H, 6.89%. Calcd for $C_{25}H_{30}O_7$: C, 67.86; H, 6.83%.

(*Z*)-3-[(2*R*,3*R*,5*S*)-3-Benzyloxy-5-methoxyoxolan-2-yl]-4-(4-methoxybenzyloxy)but-2-en-1-ol (15*Z*) and Its (*E*)-Isomer (15*E*). To a solution of ester **14** (ca. 15:1 mixture, 1.50 g, 3.39 mmol) in toluene (30 mL) was added dropwise DIBAL-H (1.01 M solution in toluene, 8.39 mL, 8.47 mmol) at −78 °C. After being stirred at −78 °C for 15 min, the reaction mixture was quenched by addition of MeOH, diluted with Et_2O, and washed with 1 M aqueous HCl solution. The aqueous layer was re-extracted with Et_2O. The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (50 g silica gel, 1:1 EtOAc–hexane as an eluent) to afford first the *Z*-isomer of allylic alcohol **15*Z*** (83 mg, 6%) as a colorless syrup: R_f = 0.16 (1:1 EtOAc–hexane); $[\alpha]_D^{25.0}$ +16.4 (*c* 0.82, $CHCl_3$); IR (neat) 1040, 1100, 1250, 1515, 1615, 2860, 2910, 3440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (ddd, 1H, *J* = 2.7, 6.1 and 14.1 Hz), 2.24 (ddd, 1H, *J* = 2.4, 5.6 and 14.1 Hz), 3.31 (s, 3H), 3.76 (s, 3H), 4.00 (bs, 2H), 4.06–4.17 (m, 2H), 4.28 (dd, 1H, *J* = 7.8 and 12.4 Hz), 4.33 (d, 1H, *J* = 11.9 Hz), 4.37 (d, 1H, *J* = 11.7 Hz), 4.41 (d, 1H, *J* = 11.7 Hz), 4.43 (d, 1H, *J* = 11.9 Hz), 4.72 (d, 1H, *J* = 4.3 Hz), 5.14 (dd, 1H, *J* = 2.7 and 5.6 Hz), 6.01 (bdd, 1H, *J* = 7.8 and 7.8 Hz), 6.82 (d, 2H, *J* = 8.8 Hz), 7.17–7.29 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.0, 55.25, 55.30, 58.4, 71.6, 71.7, 72.6, 79.5 (2C), 103.8, 113.7, 127.7, 127.8, 128.4, 129.2, 130.2, 130.4, 134.8, 137.7, 159.1; FAB-MS *m/z* 415 (M + H, 3.4%), 397 (6.6), 121 (100); FAB-HRMS Calcd for $C_{24}H_{31}O_6$ (M + H)$^+$: 415.2121, Found: *m/z* 415.2113.

Further elution gave the *E*-isomer **15*E*** (1.31 g, 93%) as a colorless syrup: R_f = 0.14 (1:1 EtOAc–hexane); $[\alpha]_D^{25.0}$ +28.7 (*c* 1.48, $CHCl_3$); IR (neat) 1050, 1100, 1175, 1250, 1455, 1515, 1615, 2860, 2910, 2930, 3445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.11 (ddd, 1H, *J* = 2.4, 6.2 and 13.9 Hz), 2.22 (ddd, 1H, *J* = 3.6, 5.3 and 13.9 Hz), 3.36 (s, 3H), 3.80 (s, 3H), 4.01 (d, 1H, *J* = 11.9 Hz), 4.13 (d, 1H, *J* = 11.9 Hz), 4.17–4.21 (m, 3H), 4.33 (d, 1H, *J* = 11.9 Hz), 4.36 (d, 1H, *J* = 11.2 Hz), 4.447 (d, 1H, *J* = 11.2 Hz), 4.451 (d, 1H, *J* = 11.9 Hz), 4.59 (bd, 1H, *J* = 4.6 Hz), 5.17 (dd, 1H, *J* = 2.4 and 5.3 Hz), 6.75 (bt, 1H, *J* = 6.8 Hz), 6.86 (d, 2H, *J* = 8.5 Hz), 7.20–7.33 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.7, 55.2 (2C), 58.8, 66.2, 71.4, 72.2, 79.3, 82.0, 103.9, 113.8, 127.5, 127.6, 128.3, 129.5, 129.9, 130.5, 136.1, 137.9, 159.2; FAB-MS *m/z* 415 (M + H, 2.6%), 383 (3.3), 121 (100); FAB-HRMS Calcd for $C_{24}H_{31}O_6$ (M + H)$^+$: 415.2121, Found: *m/z* 415.2123.

A Mixture of *N*-{(*S*)-2-[(2*R*,3*R*,5*S*)-3-Benzyloxy-5-methoxyoxolan-2-yl]-1-(4-methoxybenzyloxy)-3-buten-2-yl}trichloroacetamide (16*S*) and Its (*R*)-Isomer (16*R*). To a solution of allylic alcohol **15*E*** (1.56 g, 3.77 mmol) in CH_2Cl_2 (20 mL) were added trichloroacetonitrile (0.756 mL, 7.54 mol) and DBU (0.0564 mL, 0.377 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. The reaction mixture was concentrated to give a residue, which was passed through a short column (10 g silica gel, 1:3 EtOAc–hexane containing 1 vol% Et_3N as an eluent) to afford a crude trichloroacetimidate **6*E*** (2.14 g) as a yellow syrup. This was used for the next reaction without further purification: R_f = 0.67 (1:1 EtOAc–hexane).

To a solution of the crude imidate **6*E*** (2.14 g) in *o*-xylene (214 mL) was added solid K_2CO_3 (581 mg). Then the mixture was heated at 140 °C for 60 h, in sealed tubes under Ar. The reaction mixture was concentrated to give a residue, which was purified by column chromatography (80 g silica gel, 1:20 EtOAc–toluene as an eluent) to afford a mixture (in a ratio of ca. 7:1) of rearranged product **16*S*** and **16*R*** (1.91 g, 90% for 2 steps) as a light yellow syrup.

A small amount of the mixture was separated by PLC (1:9 EtOAc–hexane as an eluent) to provide each diastereomer in pure

form and for use as analytical samples.

16*S*: R_f = 0.44 (1:3 EtOAc–hexane); $[\alpha]_D^{24.0}$ +11.2 (*c* 1.16, $CHCl_3$); IR (neat) 1045, 1105, 1250, 1515, 1720, 2835, 2930, 3330 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.96 (ddd, 1H, *J* = 3.6, 5.2 and 14.6 Hz), 2.39 (dd, 1H, *J* = 5.9 and 14.4 Hz), 3.35 (s, 3H), 3.78 (s, 3H), 3.85 (d, 1H, *J* = 8.8 Hz), 4.14 (bdd, 1H, *J* = 3.6 and 5.2 Hz), 4.22–4.52 (m, 6H), 5.23 (dd, 1H, *J* = 3.6 and 5.9 Hz), 5.26 (bd, 1H, *J* = 11.0 Hz), 5.35 (bd, 1H, *J* = 17.6 Hz), 6.05 (dd, 1H, *J* = 11.0 and 17.6 Hz), 6.94 (d, 2H, *J* = 8.8 Hz), 7.21–7.31 (m, 7H), 8.30 (bs, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.2, 55.2, 55.4, 62.6, 70.6, 71.6, 73.2, 78.0, 79.9, 93.1, 103.7, 113.7, 115.9, 128.3, 128.5, 128.9, 129.1, 130.4, 134.4, 136.6, 159.1, 160.7; EI-MS *m/z* 559 (M + 2, 0.2%), 557 (M^+, 0.2), 528 (0.3), 526 (0.3), 468 (0.3), 466 (0.3), 388 (4.6), 387 (20.7), 386 (6.8), 385 (30.2), 121 (100); EI-HRMS Calcd for $C_{26}H_{30}{}^{35}Cl_3NO_6$ (M^+): 557.1138, Found: *m/z* 557.1141. Found: C, 56.23; H, 5.28; N, 2.42%. Calcd for $C_{26}H_{30}Cl_3NO_6$: C, 55.88; H, 5.41; N, 2.51%.

16*R*: R_f = 0.44 (1:3 EtOAc–hexane); $[\alpha]_D^{22.0}$ −2.9 (*c* 1.62, $CHCl_3$); IR (neat) 1050, 1110, 1250, 1515, 1715, 2870, 2930, 3330, 3400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.87 (ddd, 1H, *J* = 3.4, 5.1 and 14.4 Hz), 2.28 (bdd, 1H, *J* = 5.8 and 14.4 Hz), 3.27 (s, 3H), 3.71 (s, 3H), 3.74 (d, 1H, *J* = 8.8 Hz), 3.96 (d, 1H, *J* = 11.0 Hz), 3.99 (d, 1H, *J* = 8.8 Hz), 4.04 (d, 1H, *J* = 3.4 Hz), 4.13 (bdd, 1H, *J* = 3.4 and 5.1 Hz), 4.19 (d, 1H, *J* = 11.4 Hz), 4.28 (d, 1H, *J* = 11.0 Hz), 4.36 (d, 1H, *J* = 11.4 Hz), 5.13 (dd, 1H, *J* = 3.4 and 5.8 Hz), 5.20 (d, 1H, *J* = 11.0 Hz), 5.27 (d, 1H, *J* = 17.6 Hz), 6.11 (dd, 1H, *J* = 11.0 and 17.6 Hz), 6.80 (d, 2H, *J* = 8.8 Hz), 7.05–7.24 (m, 7H), 8.15 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.1, 55.2, 55.5, 61.1, 70.1, 71.1, 73.2, 79.4, 80.5, 93.0, 103.2, 113.8, 115.2, 128.1, 128.4, 128.6, 129.7, 129.8, 136.4, 136.8, 159.3, 160.5; EI-MS *m/z* 559 (M + 2, 0.1%), 557 (M^+, 0.1), 528 (0.1), 526 (0.1), 388 (0.4), 387 (1.6), 386 (0.7), 385 (2.4), 121 (100); EI-HRMS Calcd for $C_{26}H_{30}{}^{35}Cl_3NO_6$ (M^+): 557.1138, Found: *m/z* 557.1138. Found: C, 56.22; H, 5.27; N, 2.44%. Calcd for $C_{26}H_{30}Cl_3NO_6$: C, 55.88; H, 5.41; N, 2.51%.

Overman rearrangement of *Z*-allylic imidate **6*Z*** derived from allylic alcohol **15*Z*** was carried out by the same procedure to afford **16*S*** and **16*R*** in 1:5 ratio (70% yield).

A Mixture of *N*-{(*S*)-1-Hydroxy-3-(4-methoxybenzyloxy)-2-[(2*R*,3*R*,5*S*)-3-benzyloxy-5-methoxyoxolan-2-yl]propan-2-yl}trichloroacetamide (17*S*) and Its (*R*)-Isomer (17*R*). Ozone was introduced into a solution of a mixture (ca. 7:1) of the rearranged products **16*S*** and **16*R*** (289 mg, 0.516 mmol) in MeOH (5.6 mL) at −78 °C for 9 min. After the complete consumption of the starting material had been confirmed (TLC analysis), excess ozone was purged by a stream of argon gas. To this solution was added portionwise $NaBH_4$ (78.1 mg, 2.07 mmol) at −78 °C. The resulting mixture was stirred at 0 °C for 15min, then quenched by addition of 1 M aqueous HCl solution. The products were extracted with EtOAc and the combined organic layer was washed successively with saturated $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (15 g silica gel, 1:4 EtOAc–hexane as an eluent) to afford a mixture (ca. 8:1) of amides **17*S*** and **17*R*** (206 mg, 71%) as a colorless syrup.

A small amount of the mixture was separated by PLC (1:9 EtOAc–hexane as an eluent) to give each diastereomer in pure form and for use as analytical samples.

17*S*: R_f = 0.36 (1:2 EtOAc–hexane); $[\alpha]_D^{22.0}$ +25.0 (*c* 0.71, $CHCl_3$); IR (neat) 1040, 1110, 1175, 1250, 1455, 1505, 1520, 1615, 1715, 2840, 2935, 3005, 3380, 3460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.02 (ddd, 1H, *J* = 3.6, 4.6 and 14.6 Hz), 2.42 (dd, 1H, *J* = 5.7 and 14.6 Hz), 3.34 (s, 3H), 3.53 (dd, 1H, *J* = 3.4 and 10.0 Hz), 3.71 (d, 1H, *J* = 8.8 Hz), 3.80 (s, 3H), 3.89 (dd, 1H, *J* = 10.0 and 11.7 Hz), 4.23–4.27 (m, 3H), 4.29 (d, 1H, *J* = 11.2 Hz), 4.44 (d, 1H, *J* = 11.4 Hz), 4.45 (bs, 1H), 4.48 (d, 1H, *J* = 11.2 Hz), 4.56 (d, 1H, *J* = 11.4 Hz), 5.20 (dd, 1H, *J* = 3.6 and 5.7 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 7.24 (d, 2H, *J* = 8.5 Hz), 7.29–7.36 (m, 5H), 7.87 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.2, 55.3, 55.5, 61.9, 63.6, 68.8, 71.2, 73.4, 77.6, 78.9, 92.9, 103.4, 113.8, 128.2, 128.45, 128.54, 129.3, 129.8, 136.7, 159.3, 161.5; EI-MS *m/z* 563 (M + 2, 0.6%), 561 (M^+, 0.9), 527 (4.2), 525 (5.4), 391 (100), 389 (93.8); EI-HRMS Calcd for $C_{25}H_{30}{}^{35}Cl_3NO_7$ (M^+): 561.1087, Found: *m/z* 561.1083.

17*R*: R_f = 0.32 (1:2 EtOAc–hexane); $[\alpha]_D^{19.0}$ −23.4 (*c* 0.60, $CHCl_3$); IR (neat) 1045, 1105, 1250, 1515, 1715, 2870, 2930, 2950, 3300, 3400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.95 (ddd, 1H, *J* = 3.5, 5.4 and 14.6 Hz), 2.32 (dd, 1H, *J* = 5.9 and 14.6 Hz), 3.35 (s, 3H), 3.59 (d, 1H, *J* = 9.3 Hz), 3.92 (d, 1H, *J* = 9.3 Hz), 3.79 (s, 3H), 3.93 (d, 1H, *J* = 9.3 Hz), 4.08 (d, 1H, *J* = 10.7 Hz), 4.10 (d, 1H, *J* = 2.7 Hz), 4.22–4.25 (m, 1H), 4.27 (d, 1H, *J* = 9.3 Hz), 4.30 (d, 1H, *J* = 11.2 Hz), 4.36 (d, 1H, *J* = 10.7 Hz), 4.51 (d, 1H, *J* = 11.2 Hz), 5.19 (dd, 1H, *J* = 2.9 and 5.7 Hz), 6.89 (d, 2H, *J* = 8.7 Hz), 7.13–7.33 (m, 7H), 8.55 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.0, 55.3, 55.5, 63.3, 64.5, 68.6, 71.5, 73.4, 80.0, 80.2, 93.0, 103.7, 113.8, 128.4, 128.55, 128.64, 128.9, 129.7, 136.3, 159.4, 162.5; EI-MS *m/z* 563 (M + 2, 1.1%), 561 (M^+, 1.4), 527 (6.4), 525 (8.8), 412 (2.2), 391 (100), 389 (100); EI-HRMS Calcd for $C_{25}H_{30}{}^{35}Cl_3NO_7$ (M^+): 561.1087, Found: *m/z* 561.1088.

(*S*)-4-[(2*R*,3*R*,5*S*)-3-Benzyloxy-5-methoxyoxolan-2-yl]-4-(4-methoxybenzyloxymethyl)-1,3-oxazolidin-2-one (18*S*) and Its (*R*)-Isomer (18*R*). To a solution of the mixture (ca. 8:1) of amides **17*S*** and **17*R*** (186 mg, 0.330 mmol) in CH_2Cl_2 (4 mL) was added DBU (0.010 mL, 0.0660 mmol) and the mixture was stirred at 25 °C for 2 h. Removal of the solvent gave a residue, which was purified by column chromatography (8 g silica gel, 1:2 EtOAc–hexane as an eluent) to afford *S*-isomer **18*S*** (16.4 mg, 11%) as a pale yellow syrup: R_f = 0.39 (2:1 EtOAc–hexane); $[\alpha]_D^{26.0}$ +37.4 (*c* 0.87, $CHCl_3$); IR (neat) 1050, 1110, 1180, 1250, 1360, 1515, 1615, 1745, 1770, 1780, 2910, 3000, 3320, 3440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.04 (ddd, 1H, *J* = 2.9, 4.9 and 13.7 Hz), 2.27 (ddd, 1H, *J* = 1.6, 5.7 and 13.7 Hz), 3.34 (s, 3H), 3.41 (d, 1H, *J* = 9.0 Hz), 3.47 (d, 1H, *J* = 9.0 Hz), 3.79 (s, 3H), 4.04 (d, 1H, *J* = 11.0 Hz), 4.04–4.09 (m, 2H), 4.25 (d, 1H, *J* = 11.6 Hz), 4.31 (d, 1H, *J* = 8.5 Hz), 4.390 (d, 1H, *J* = 11.0 Hz), 4.392 (d, 1H, *J* = 11.6 Hz), 4.44 (d, 1H, *J* = 8.5 Hz), 5.18 (dd, 1H, *J* = 2.9 and 5.7 Hz), 5.56 (s, 1H), 6.89 (d, 2H, *J* = 8.8 Hz), 7.16–7.39 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.4, 55.2, 55.4, 60.6, 71.2, 72.0, 72.3, 73.1, 78.3, 78.9, 103.7, 113.9, 128.32, 128.34, 128.7, 129.2, 129.7, 136.4, 159.2, 159.5; EI-MS *m/z* 443 (M^+, 6.1%), 411 (0.9), 352 (2.0), 322 (2.0), 261 (3.9), 260 (23.2), 236 (8.7), 235 (51.6), 234 (20.4), 121 (100); EI-HRMS Calcd for $C_{24}H_{29}NO_7$ (M^+): 443.1944, Found: *m/z* 443.1944.

Further elution gave *R*-isomer **18*R*** (130 mg, 89%) as a pale yellow syrup: R_f = 0.27 (2:1 EtOAc–hexane); $[\alpha]_D^{25.5}$ +24.4 (*c* 0.67, $CHCl_3$); IR (neat) 1045, 1110, 1250, 1515, 1745, 1755, 2865, 2920, 3290 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (ddd, 1H, *J* = 2.8, 5.9 and 14.4 Hz), 2.27 (ddd, 1H, *J* = 2.0, 5.6 and 14.4 Hz), 3.34 (s, 3H), 3.44 (d, 1H, *J* = 9.0 Hz), 3.48 (d, 1H, *J* = 9.0 Hz), 3.80 (s, 3H), 3.86 (d, 1H, *J* = 9.4 Hz), 3.94–3.98 (m, 1H), 3.98 (d, 1H, *J* = 11.5 Hz), 4.21 (d, 1H, *J* = 4.4 Hz), 4.26 (d, 1H, *J*

= 11.4 Hz), 4.37 (d, 1H, J = 11.5 Hz), 4.43 (d, 1H, J = 11.4 Hz), 4.56 (d, 1H, J = 9.4 Hz), 5.18 (dd, 1H, J = 2.8 and 5.6 Hz), 5.35 (s, 1H), 6.88 (d, 2H, J = 8.6 Hz), 7.13–7.37 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.4, 55.3, 55.4, 61.6, 68.8, 70.9, 72.9, 73.2, 77.8, 79.8, 104.0, 113.9, 127.9, 128.1, 128.5, 129.3, 129.7, 136.9, 158.5, 159.5; EI-MS m/z 443 (M^+, 4.7%), 411 (0.7), 352 (3.6), 322 (0.9), 293 (3.7), 292 (23.0), 261 (4.2), 260 (26.5), 236 (4.9), 235 (33.8), 121 (99.7), 91 (100); EI-HRMS Calcd for $C_{24}H_{29}NO_7$ (M^+): 443.1944, Found: m/z 443.1944.

(2*R*,4*R*,5*R*,6*R*)-4-Benzyloxy-2,5-diacetoxy-6-(4-methoxybenzyloxymethyl)-1-aza-8-oxabicyclo[4.3.0]nonan-9-one (19). To a solution of oxazolidinone **18*R*** (23.2 mg, 0.0523 mmol) in THF (1.0 mL) was added 2 M aqueous HCl solution (1.0 mL). The resulting mixture was stirred at 25 °C for 12 h, and then poured into saturated aqueous $NaHCO_3$ solution. The products were extracted with $CHCl_3$, and then dried. Removal of the solvent gave a residue, which was dissolved in pyridine (0.5 mL) and Ac_2O (0.5 mL). After being stirred at 25 °C for 12 h, the resulting solution was diluted with EtOAc, and washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (1.5 g silica gel, 1:2 EtOAc–hexane as an eluent) to afford diacetate **19** (30.5 mg, 97%) as a pale yellow syrup: R_f = 0.46 (2:1 EtOAc–hexane); $[\alpha]_D^{22.5}$ −21.0 (c 0.26, $CHCl_3$); IR (neat) 1020, 1080, 1180, 1220, 1370, 1415, 1515, 1615, 1730, 1770, 1790, 2875, 2940, 3020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (ddd, 1H, J = 4.1, 11.3 and 14.2 Hz), 1.97 (s, 3H), 2.00 (s, 3H), 2.41 (ddd, 1H, J = 2.0, 4.8 and 14.2 Hz), 3.58 (d, 1H, J = 10.0 Hz), 3.68 (d, 1H, J = 10.0 Hz), 3.80 (s, 3H), 3.89 (ddd, 1H, J = 4.8, 9.8 and 11.3 Hz), 4.25 (d, 1H, J = 8.8 Hz), 4.35 (d, 1H, J = 8.8 Hz), 4.44 (d, 1H, J = 11.6 Hz), 4.54 (d, 1H, J = 11.6 Hz), 4.55 (d, 1H, J = 11.7 Hz), 4.65 (d, 1H, J = 11.7 Hz), 4.97 (d, 1H, J = 9.8 Hz), 6.85 (dd, 1H, J = 2.0 and 4.1 Hz), 6.88 (d, 2H, J = 8.7 Hz), 7.20 (d, 2H, J = 8.7 Hz), 7.24–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 21.0, 34.4, 55.3, 62.2, 70.0, 71.5, 71.6, 72.4, 73.4, 74.4, 76.7, 113.9, 127.3, 127.9, 128.5, 128.9, 129.3, 137.7, 155.0, 159.4, 168.6, 170.2; EI-MS m/z 514 (M + H, 9.7%), 454 (30.3), 304 (4.9), 303 (100); EI-HRMS Calcd for $C_{27}H_{32}NO_9$ (M + H)$^+$: 514.2077, Found: m/z 514.2075.

N*-{(*S*)-1-[(2*R*,3*R*,5*S*)-3-Benzyloxy-5-methoxyoxolan-2-yl]-1-formyl-2-(4-methoxybenzyloxy)ethyl}trichloroacetamide (20).** Ozone was introduced into a solution of the mixture of rearranged products **16*S and **16*R*** (ca. 7:1, 600 mg, 1.07 mmol) in MeOH (12 mL) at −78 °C for 15 min. After the complete consumption of the starting material had been confirmed (TLC analysis), excess ozone was removed by a stream of argon gas. To the reaction mixture was added Me_2S (0.79 mL, 10.7 mmol) at −78 °C, and the resulting mixture was stirred at 0 °C for 2 h. Removal of the solvent gave a residue, which was purified by column chromatography (50 g silica gel, 1:39 EtOAc–toluene as an eluent) to afford *R*-isomer **20*R*** (72.8 mg, 12%) as a pale yellow syrup: R_f = 0.51 (1:3 EtOAc–hexane, 2 times); $[\alpha]_D^{24.5}$ +32.3 (c 0.37, $CHCl_3$); IR (neat) 1045, 1105, 1250, 1505, 1515, 1615, 1715, 1730, 2870, 2930, 2950, 3360, 3450 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (ddd, 1H, J = 4.0, 4.9 and 14.4 Hz), 2.30 (dd, 1H, J = 5.6 and 14.4 Hz), 3.33 (s, 3H), 3.79 (s, 3H), 4.08 (d, 1H, J = 10.2 Hz), 4.17–4.21 (m, 3H), 4.38 (d, 1H, J = 11.2 Hz), 4.40 (d, 1H, J = 11.4 Hz), 4.46 (d, 1H, J = 11.4 Hz), 4.53 (d, 1H, J = 3.2 Hz), 5.19 (dd, 1H, J = 4.0 and 5.6 Hz), 6.86 (d, 2H, J = 8.5 Hz), 7.13–7.33 (m, 7H), 8.60 (bs, 1H), 9.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.7, 55.3, 55.7, 69.8 (2C), 71.5, 73.4, 79.5, 79.9, 93.1, 104.4, 113.8, 128.2, 128.47, 128.50, 129.4, 129.6, 136.5, 159.3, 161.8, 195.8; EI-MS m/z 563 (M + 4, 0.3%), 561 (M + 2, 0.3), 559 (M^+, 0.4), 527 (0.7), 525 (2.0), 523 (3.0), 442 (0.3), 440 (0.6), 438 (0.7), 389 (6.4), 387 (9.3), 338 (30.9), 337 (15.8), 336 (95.2), 335 (20.9), 334 (100); EI-HRMS Calcd for $C_{25}H_{28}{}^{35}Cl_3NO_7$ (M^+): 559.0931, Found: m/z 559.0936.

Further elution gave *S*-isomer **20*S*** (486 mg, 81%) as a colorless syrup: R_f = 0.48 (1:3 EtOAc–hexane, 2 times); $[\alpha]_D^{23.5}$ +16.6 (c 1.26, $CHCl_3$); IR (neat) 1045, 1110, 1250, 1505, 1515, 1615, 1715, 1735, 2840, 2930, 3360 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13 (ddd, 1H, J = 2.9, 5.9 and 14.4 Hz), 2.37 (ddd, 1H, J = 1.9, 5.6 and 14.4 Hz), 3.36 (s, 3H), 3.85 (s, 3H), 4.13 (d, 1H, J = 9.6 Hz), 4.29 (ddd, 1H, J = 1.9, 4.1 and 5.9 Hz), 4.34 (d, 1H, J = 12.2 Hz), 4.38 (d, 1H, J = 9.6 Hz), 4.45 (d, 1H, J = 11.7 Hz), 4.52 (d, 1H, J = 12.2 Hz), 4.53 (d, 1H, J = 11.7 Hz), 4.73 (d, 1H, J = 4.1 Hz), 5.20 (dd, 1H, J = 2.9 and 5.6 Hz), 6.91 (d, 2H, J = 8.8 Hz), 7.22–7.42 (m, 7H), 8.07 (bs, 1H), 9.82 (s, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 39.2, 55.3, 55.4, 66.3, 68.7, 71.5, 73.3, 78.5, 78.9, 92.7, 103.6, 113.9, 128.3, 128.67, 128.71, 129.4, 129.6, 136.7, 159.4, 161.1, 197.3; EI-MS m/z 563 (M + 4, 0.02%), 561 (M + 2, 0.03), 559 (M^+, 0.03), 532 (0.07), 530 (0.1), 528 (0.1), 525 (0.2), 523 (0.3), 389 (0.8), 387 (1.2), 339 (0.9), 338 (5.9), 337 (3.1), 336 (18.1), 335 (4.0), 334 (19.1), 121 (100); EI-HRMS Calcd for $C_{25}H_{28}{}^{35}Cl_3NO_7$ (M^+): 559.0931, Found: m/z 559.0925.

Methyl (*S*)-2-[(2*R*,3*R*,5*S*)-3-Benzyloxy-5-methoxyoxolan-2-yl]-3-(4-methoxybenzyloxy)-2-(trichloroacetamido)propanoate (22). To a solution of aldehyde **20*S*** (390 mg, 0.696 mmol) in a mixed solvent of *t*-BuOH–H_2O (1:1, 8 mL) were added successively $NaH_2PO_4{\cdot}2H_2O$ (217 mg, 1.39 mmol), $HOSO_2NH_2$ (203 mg, 2.09 mmol) and $NaClO_2$ (189 mg, 2.09 mmol) at 0 °C. After stirring at 25 °C for 15 min, 20 wt% aqueous $Na_2S_2O_3$ solution was added to the reaction mixture until the yellow color of the mixture disappeared. The products were extracted with $CHCl_3$, and then dried. Removal of the solvent afforded crude carboxylic acid **21** (401 mg, 100%) as a colorless oil, which was used for the next reaction without further purification: R_f = 0.35 (1:9 MeOH–$CHCl_3$).

To a stirring solution of this crude carboxylic acid **21** in MeOH (8 mL) was added $TMSCHN_2$ (2.0 M in hexane, 1.75 mL, 3.48 mmol) at 25 °C and the mixture was stirred at 25 °C for 1 h. Removal of the solvent gave a residue, which was purified by column chromatography (25 g silica gel, 1:19 EtOAc–toluene as an eluent) to afford ester **22** (405 mg, 98% for 2 steps) as a pale yellow syrup: R_f = 0.69 (1:3 EtOAc–toluene); $[\alpha]_D^{25.0}$ +50.6 (c 1.26, $CHCl_3$); IR (neat) 1050, 1105, 1250, 1515, 1615, 1730, 1740, 2840, 2950, 3390 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (ddd, 1H, J = 4.9, 4.9 and 13.7 Hz), 2.16 (ddd, 1H, J = 2.2, 6.6 and 13.7 Hz), 3.30 (s, 3H), 3.62 (s, 3H), 3.79 (s, 3H), 4.03 (d, 1H, J = 9.4 Hz), 4.31 (d, 1H, J = 11.0 Hz), 4.41–4.44 (m, 1H), 4.44 (d, 1H, J = 11.0 Hz), 4.45 (d, 1H, J = 11.9 Hz), 4.56 (d, 1H, J = 11.9 Hz), 4.66 (d, 1H, J = 6.1 Hz), 4.73 (d, 1H, J = 9.4 Hz), 5.15 (dd, 1H, J = 2.2 and 4.9 Hz), 6.84 (d, 2H, J = 8.5 Hz), 7.18–7.36 (m, 7H), 7.85 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.2, 52.6, 55.1, 55.2, 66.9, 69.4, 72.5, 72.9, 79.1, 79.3, 93.5, 103.9, 113.6, 128.2, 128.4, 128.5, 129.1, 130.1, 136.6, 159.1, 160.1, 170.2; EI-MS m/z 593 (M + 4, 0.2%), 591 (M + 2, 0.4), 589 (M^+, 0.4), 562 (0.5), 560 (1.3), 558 (1.3), 555 (1.1), 553 (1.6), 422 (3.8), 421 (16.7), 420 (13.6), 419 (67.8), 418 (20.3), 417 (100); EI-HRMS Calcd for $C_{26}H_{30}{}^{35}Cl_3NO_8$ (M^+): 589.1036, Found: m/z 589.1037.

An Equilibrium Mixture of Methyl (*S*)-2-[(2*R*,3*R*,5*R*&*S*)-3-

Benzyloxy-5-hydroxyoxolan-2-yl]-3-(4-methoxybenzyloxy)-2-(trichloroacetamido)propanoate (5). A solution of methyl glycoside **22** (405 mg, 0.685 mL) in a mixed solvent (2 mL of 4 M aqueous HCl solution and 6 mL of THF) was stirred at 25 °C for 10 h. The resulting solution was cooled to 0 °C and neutralized carefully with 25% aqueous $NaHCO_3$ solution. The products were extracted with $CHCl_3$. Removal of the solvent gave a residue, which was purified by column chromatography (16 g silica gel, 2:5 EtOAc–hexane as an eluent) to give first the starting material **22** (44.2 mg, 11%). Further elution (2:3 EtOAc–hexane as an eluent) gave lactol **5** (298 mg, 76%) as a mixture of anomers (α:$\beta \sim$ 1:1): R_f = 0.37 (1:1 EtOAc–hexane); $[\alpha]_D^{25.0}$ +6.6 (*c* 0.89, CH_3OH, after 12 h at 25 °C); IR (neat) 1050, 1100, 1170, 1245, 1300, 1360, 1455, 1505, 1520, 1540, 1615, 1715, 1730, 2870, 2950, 3010, 3390, 3450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, after 12 h) δ 2.02-2.30 (m, 2H), 3.04 (bs, 0.5H), 3.47 (d, 0.5H, J = 9.0 Hz), 3.62 (s, 1.5H), 3.68 (s, 1.5H), 3.80 (s, 3H), 3.99 (d, 0.5H, J = 8.8 Hz), 4.05 (d, 0.5H, J = 8.8 Hz), 4.30–4.52 (m, 2H), 4.40–4.49 (m, 3H), 4.59 (d, 0.5H, J = 8.8 Hz), 4.62 (d, 0.5H, J = 4.8 Hz), 4.68 (d, 0.5H, J = 8.8 Hz), 4.79 (d, 0.5H, J = 5.1 Hz), 5.51 (dd, 0.5H, J = 4.9 and 9.0 Hz), 5.69 (m, 0.5H), 6.82 (d, 2H, J = 8.5 Hz), 7.27–7.38 (m, 7H), 7.80 (bs, 0.5H), 7.91 (bs, 0.5H); EI-MS *m*/*z* 577 (M + 2, 1.7%), 575 (M^+, 5.0), 415 (23.0), 413 (29.4), 405 (33.8), 404 (12.4), 403 (54.1), 277 (100); EI-HRMS Calcd for $C_{25}H_{28}{}^{35}Cl_3NO_8$ (M^+): 575.0880, Found: *m*/*z* 575.0880.

1-Ethyl 8-Methyl (*E*,5*R*,6*R*,7*S*)-5-Benzyloxy-6-hydroxy-7-(4-methoxybenzyloxymethyl)-7-(trichloroacetamido)oct-2-enedioate (23). To a solution of lactol **5** (298 mg, 0.517 mmol) in toluene (6 mL) was added $Ph_3P{=}CHCO_2Et$ (216 mg, 0.620 mmol) and the mixture was stirred at 25 °C for 20 h. Removal of the solvent gave a residue, which was purified by column chromatography (15 g silica gel, 1:7 EtOAc–hexane as an eluent) to afford **23** (299 mg, 89%) as a pale yellow syrup: R_f = 0.54 (1:2 EtOAc–hexane); $[\alpha]_D^{21.5}$ +7.9 (*c* 0.95, $CHCl_3$); IR (neat) 1040, 1070, 1175, 1250, 1505, 1515, 1715, 1720, 1740, 2840, 2900, 2955, 3360, 3400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7.1 Hz), 2.50–2.72 (m, 2H), 3.52-3.58 (m, 1H), 3.54 (s, 3H), 3.80 (s, 3H), 3.83 (d, 1H, J = 8.5 Hz), 4.03 (d, 1H, J = 10.5 Hz), 4.12 (dd, 1H, J = 1.4, and 8.5 Hz), 4.18 (q, 2H, J = 7.1 Hz), 4.30 (d, 1H, J = 10.5 Hz), 4.38 (d, 1H, J = 11.2 Hz), 4.42 (d, 1H, J = 11.7 Hz), 4.48 (d, 1H, J = 11.7 Hz), 4.55 (d, 1H, J = 11.2 Hz), 5.90 (bd, 1H, J = 15.6 Hz), 6.80–6.91 (m, 3H), 6.86 (d, 2H, J = 8.5 Hz), 7.19 (d, 2H, J = 8.5 Hz), 7.25–7.35 (m, 5H), 8.06 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 33.3, 52.9, 55.2, 60.4, 66.3, 68.3, 72.0, 73.4, 73.8, 92.2, 113.9, 124.5, 128.0, 128.0, 128.4, 129.2, 129.39, 129.44, 137.0, 143.3, 159.4, 161.7, 166.0, 169.2; EI-MS *m*/*z* 649 (M + 4, 0.3%), 647 (M + 2, 0.9), 645 (M^+, 0.8), 612 (1.8), 611 (4.6), 610 (1.6), 609 (6.2), 528 (1.1), 527 (0.8), 526 (1.8), 525 (1.0), 524 (2.0), 478 (4.5), 477 (14.0), 476 (17.0), 475 (5.4), 474 (26.8), 473 (100); EI-HRMS Calcd for $C_{29}H_{34}{}^{35}Cl_3NO_9$ (M^+): 645.1298, Found: *m*/*z* 645.1294.

Methyl (*E*,2*S*,3*R*,4*R*)-4-Benzyloxy-3,8-dihydroxy-2-(4-methoxybenzyloxymethyl)-2-(trichloroacetamido)oct-6-enoate (24). To a solution of diester **23** (299 mg, 0.462 mmol) in THF (12 mL) was added dropwise DIBAL-H (1.01 M solution in toluene, 0.915 mL, 0.924 mmol) at −18 °C. The resulting mixture was stirred at −18 °C for 15 min, and then quenched by addition of 1 M aqueous HCl solution. The products were extracted with Et_2O, and the combined organic layer was washed successively with saturated aqueous $NaHCO_3$ solution and brine, then dried. Removal of the solvent gave a residue, which was purified by column chromatography (20 g silica gel, 1:2 EtOAc–hexane as an eluent) to afford allylic alcohol **24** (228 mg, 82%) as a colorless syrup: R_f = 0.31 (1:1 EtOAc–hexane); $[\alpha]_D^{24.0}$ +3.5 (*c* 1.31, $CHCl_3$); IR (neat) 1070, 1090, 1250, 1300, 1505, 1515, 1715, 1730, 2870, 2950, 3390, 3470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.69 (bs, 1H), 2.48 (bdd, 2H, J = 7.3 and 7.3 Hz), 3.47–3.54 (m, 1H), 3.52 (s, 3H), 3.67 (d, 1H, J = 9.0 Hz), 3.80 (s, 3H), 4.00–4.05 (m, 2H), 4.04 (d, 1H, J = 10.5 Hz), 4.19 (dd, 1H, J = 1.2 and 9.0 Hz), 4.32 (d, 1H, J = 10.5 Hz), 4.37 (d, 1H, J = 11.0 Hz), 4.41 (d, H, J = 11.4 Hz), 4.49 (d, H, J = 11.4 Hz), 4.59 (d, 1H, J = 11.0 Hz), 5.56 (bdt, 1H, J = 15.4 and 7.3 Hz), 5.73 (bdt, 1H, J = 15.4 and 5.5 Hz), 6.86 (d, 2H, J = 8.5 Hz), 7.19 (d, 2H, J = 8.5 Hz), 7.24–7.35 (m, 5H), 8.06 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.0, 52.8, 55.3, 63.2, 66.2, 68.1, 71.5, 73.1, 73.5, 76.7, 92.3, 113.9, 126.8, 127.9 (2C), 128.3, 129.3, 129.4, 133.0, 137.4, 159.4, 161.7, 169.4; FAB-MS *m*/*z* 608 (M + 5, 44.2%), 607 (M + 4, 30.0), 606 (M + 3, 82.3), 605 (M + 2, 33.0), 604 (M + H, 81.0), 301 (100); FAB-HRMS Calcd for $C_{27}H_{33}{}^{35}Cl_3NO_8$ ($M + H)^+$: 604.1271, Found: *m*/*z* 604.1274.

Methyl (4*S*,5*R*)-5-[(*E*,*R*)-1-Benzyloxy-5-hydroxypent-3-en-1-yl]-4-(4-methoxybenzyloxymethyl)-2-oxooxazolidine-4-carboxylate (25). To a solution of amide **24** (182 mg, 0.301 mmol) in CH_2Cl_2 (3.6 mL) was added dropwise DBU (0.0045 mL, 0.0301 mmol) at 0 °C and the mixture was stirred at 25 °C for 20 h. Removal of the solvent gave a residue, which was purified by column chromatography (8 g silica gel, 3:2 EtOAc–hexane as an eluent) to afford oxazolidinone **25** (126 mg, 86%) as a colorless syrup: R_f = 0.30 (3:1 EtOAc–hexane); $[\alpha]_D^{22.5}$ −85.8 (*c* 0.63, $CHCl_3$); IR (neat) 1030, 1100, 1250, 1515, 1730, 1770, 2870, 2930, 2950, 3010, 3350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (bs, 1H), 2.47–2.64 (m, 2H), 3.34 (s, 3H), 3.52 (d, 1H, J = 8.7 Hz), 3.72 (d, 1H, J = 8.7 Hz), 3.76–3.83 (m, 1H), 3.80 (s, 3H), 4.10 (bd, 2H, J = 5.2 Hz), 4.21 (d, 1H, J = 11.9 Hz), 4.33 (d, 1H, J = 1.4 Hz), 4.46 (s, 2H), 4.64 (d, 1H, J = 11.9 Hz), 5.62 (ddd, 1H, J = 6.4, 7.9 and 15.4 Hz), 5.73 (bs, 1H), 5.79 (dt, 1H, J = 15.4 and 5.2 Hz), 6.87 (d, 2H, J = 8.8 Hz), 7.17 (d, 2H, J = 8.8 Hz), 7.20–7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.7, 52.4, 55.3, 63.2, 65.5, 70.1, 73.3, 75.1, 76.0, 80.6, 113.9, 125.9, 126.3, 127.3, 128.2, 128.9, 129.3, 133.5, 137.7, 157.0, 159.5, 170.0; FAB-MS *m*/*z* 486 (M + H, 52.2%), 469 (29.5), 468 (100); FAB-HRMS Calcd for $C_{26}H_{32}NO_8$ ($M + H)^+$: 486.2128, Found: *m*/*z* 486.2128.

Methyl (4*S*,5*R*)-5-[(*E*,*R*)-1-Benzyloxy-5-bromopent-3-en-1-yl]-4-(4-methoxybenzyloxymethyl)-2-oxooxazolidine-4-carboxylate (3). To a solution of allylic alcohol **25** (133 mg, 0.273 mmol) in CH_2Cl_2 (3 mL) was added Et_3N (0.0762 mL, 0.547 mmol). After being stirred at 25 °C for 10 min, to this solution was added MsCl (0.0423 mL, 0.547 mmol). The resulting mixture was stirred at 25 °C for 30 min, and then diluted with EtOAc and washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a crude mesylate: R_f = 0.48 (3:1 EtOAc–hexane).

To a solution of the mesylate in THF (1.5 mL) was added LiBr (119 mg, 1.37 mmol) and the mixture was stirred at 25 °C for 1 h. The resulting mixture was diluted with $CHCl_3$ and washed with H_2O, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (5 g silica gel, 2:5 EtOAc–hexane as an eluent) to afford allyl bromide **3** (135 mg, 93%) as a colorless syrup: R_f = 0.71 (3:1 EtOAc–hexane); $[\alpha]_D^{24.0}$ −72.1 (*c* 0.96, $CHCl_3$); IR (neat) 1030, 1105, 1250, 1515, 1730,

1770, 2865, 2950, 3010, 3340 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.48–2.66 (m, 2H), 3.35 (s, 3H), 3.53 (d, 1H, J = 8.8 Hz), 3.73 (d, 1H, J = 8.8 Hz), 3.79–3.85 (m, 1H), 3.81 (s, 3H), 3.93 (d, 2H, J = 7.3 Hz), 4.23 (d, 1H, J = 11.7 Hz), 4.31 (d, 1H, J = 1.4 Hz), 4.47 (s, 2H), 4.64 (d, 1H, J = 11.7 Hz), 5.71 (dt, 1H, J = 15.0 and 7.4 Hz), 5.74 (bs, 1H), 5.86 (dt, 1H, J = 15.0 and 7.3 Hz), 6.88 (d, 2H, J = 8.8 Hz), 7.18 (d, 2H, J = 8.8 Hz), 7.21–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.7, 32.3, 52.4, 55.3, 65.5, 70.2, 73.3, 75.0, 75.8, 80.6, 113.9, 126.3, 127.3, 128.2, 128.9, 129.3, 130.1, 130.6, 137.5, 156.9, 159.5, 170.0; FAB-MS m/z 550 (M + 3, 98.3), 548 (M + H, 100); FAB-HRMS Calcd for $C_{26}H_{31}{}^{79}BrNO_7$ $(M + H)^+$: 548.1283, Found: m/z 548.1282.

Dodecane-1,6-diol (26).[26] To a mixture of Mg (turnings, 258 mg, 10.6 mmol) in Et_2O (20 mL) was added 1-bromohexane (1.49 mL, 10.6 mmol). This was stirred vigorously at 25 °C for 30 min. To the resulting gray suspension was added cyclohexanone (1.0 mL, 9.65 mmol) dropwise at 25 °C. The resulting mixture was stirred at 25 °C for 2 h, and then quenched by addition of 2 M aqueous HCl solution at 0 °C. The products were extracted with Et_2O and the organic layer was washed successively with 2 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave crude *tert*-alcohol, which was used for the next reaction without further purification: R_f = 0.50 (1:3 EtOAc–hexane).

To a solution of the *tert*-alcohol in *o*-xylene (10 mL) was added I_2 (24.5 mg, 0.0965 mmol) and this was stirred under reflux for 4 h. The resulting solution was quenched by addition of 20% aqueous $Na_2S_2O_3$ solution until the red color of the reaction mixture disappeared. The products were extracted with pentane, and the organic layer was washed with 20% aqueous $Na_2S_2O_3$ solution. Pentane was evaporated off to afford a crude solution of 1-hexylcyclohex-1-ene in *o*-xylene: R_f = 0.86 (1:9 EtOAc–hexane).

The solution of the crude alkene in *o*-xylene was diluted with MeOH (10 mL), then ozone was introduced into the solution at 0 °C for 10 min. After the complete consumption of starting material was confirmed (TLC analysis), excess ozone was removed with a stream of Ar. To the mixture was added portionwise $NaBH_4$ (1.83 g, 48.2 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, then diluted with Et_2O and washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine. The aqueous layer was re-extracted with Et_2O and the combined organic layer was concentrated to give a residue, which was purified by column chromatography (30 g silica gel, 1:1 EtOAc–hexane as an eluent) to afford diol **26** (1.04 g, 53% for 3 steps) as white crystals: R_f = 0.33 (1:1 EtOAc–hexane); Mp 44.2–45.3 °C; IR (KBr) 1000, 1050, 1065, 1135, 1155, 1465, 2850, 2930, 3300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.1 Hz), 1.25–1.44 (m, 16H), 1.58 (m, 2H), 1.67 (bs, 1H), 1.69 (bs, 1H), 3.58 (bs, 1H), 3.64 (t, 2H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.4, 25.6, 25.7, 29.3, 31.8, 32.6, 37.3, 37.5, 62.8, 71.8; FAB-MS m/z 203 (M + H, 4.4%), 185 (34.5), 93 (100); FAB-HRMS Calcd for $C_{12}H_{27}O_2$ (M + H)$^+$: 203.2011, Found: m/z 203.2012.

1-Bromododecan-6-one (27). To a solution of diol **26** (1.04 g, 5.14 mmol) in CH_2Cl_2 were added Ph_3P (1.38 g, 5.25 mmol) and CBr_4 (1.72 g, 5.19 mmol) at −15 °C. The resulting mixture was stirred at 0 °C for 20 h. Removal of the solvent gave a residue, which was purified by column chromatography (30 g silica gel, 1:6 EtOAc–hexane as an eluent) to afford bromo alcohol (1.19 g, 88%) as a pale yellow oil: R_f = 0.78 (1:1 EtOAc–hexane); IR (neat) 1020, 1065, 1080, 1245, 1265, 1440, 1460, 2875, 2930, 3345 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 6.9 Hz), 1.25–1.53 (m, 16H), 1.88 (m, 2H), 3.42 (t, 2H, J = 6.9 Hz), 3.52–3.68 (bs, 1H); ^{13}C NMR (75 MHz) δ 14.1, 22.6, 24.8, 25.6, 28.2, 29.3, 31.8, 32.7, 33.8, 37.2, 37.6, 71.8; EI-MS m/z 265 (M − H + 2, 0.3%), 263 (M − H, 0.3%), 249 (0.5), 248 (3.1), 247 (0.5), 246 (3.2), 183 (0.2), 182 (3.0), 181 (45.3), 180 (4.7), 179 (47.1), 164 (1.8), 163 (12.5), 162 (1.9), 161 (12.8), 115 (100); EI-HRMS Calcd for $C_{12}H_{24}{}^{79}BrO$ (M − H): 263.1010, Found: m/z 263.1016. Found: C, 54.40; H, 9.22%. Calcd for $C_{12}H_{25}BrO$: C, 54.34; H, 9.50%.

To a suspension of bromo alcohol (1.19 g, 4.49 mmol) and Celite (2.4 g) in acetone (24 mL) was added dropwise Jones' reagent (2.67 M solution of CrO_3 in aqueous sulfuric acid solution; 1.35 mL, 3.59 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was quenched by addition of propan-2-ol until the orange-yellow color of the mixture disappeared. The insoluble material was removed by filtration through a pad of Celite; this Celite was then rinsed with EtOAc (50 mL × 5). The filtrate was washed with saturated aqueous $NaHCO_3$ solution, and then dried. Removal of the solvent gave bromo ketone **27** (1.14 g, 97%) as a yellow oil: R_f= 0.69 (1:3 EtOAc–hexane); IR (neat) 1030, 1070, 1085, 1125, 1250, 1270, 1375, 1410, 1460, 1715, 2860, 2930 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.9 Hz), 1.24–1.34 (m, 6H), 1.37–1.49 (m, 2H), 1.51–1.65 (m, 4H), 1.87 (m, 2H), 2.39 (t, 2H, J = 7.8 Hz), 2.42 (t, 2H, J = 7.8 Hz), 3.41 (t, 2H, J = 6.9 Hz); ^{13}C NMR (75 MHz) δ 14.0, 22.5, 22.8, 23.8, 27.7, 28.9, 31.6, 32.5, 33.6, 42.4, 42.9, 211.0; EI-MS m/z 264 (M + 2, 6.5%), 262 (M^+, 6.8), 208 (0.8), 207 (4.9), 206 (0.8), 205 (5.0), 184 (3.6), 183 (26.9), 181 (0.4), 180 (1.4), 179 (19.2), 178 (1.5), 177 (19.7), 113 (100); EI-HRMS Calcd for $C_{12}H_{23}{}^{79}BrO$ (M^+): 262.0932, Found: m/z 262.0932. Found: C, 54.87; H, 8.50%. Calcd for $C_{12}H_{23}BrO$: C, 54.76; H, 8.81%.

6,6-Ethylenedioxy-1-phenylsulfonyldodecane (4). To a solution of bromo ketone **27** (1.14 g, 4.33 mmol) in DMF (12 mL) was added $PhSO_2Na{\cdot}2H_2O$ (1.44 g, 7.18 mmol) and the mixture was stirred at 25 °C for 24 h. The resulting mixture was diluted with EtOAc and washed successively with saturated $NaHCO_3$ and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (60 g silica gel, 1:5 EtOAc–hexane as an eluent) to afford keto sulfone (1.19 g, 85%) as white crystals: R_f = 0.30 (1:3 EtOAc–hexane); Mp 32.8–33.9 °C; IR (KBr) 1090, 1150, 1275, 1285, 1320, 1445, 1470, 1705, 2865, 2935, 3065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$); δ 0.88 (t, 3H, J = 6.9 Hz), 1.22–1.42 (m, 8H), 1.54 (m, 4H), 1.64–1.78 (m, 2H), 2.35 (t, 2H, J = 7.5), 2.37 (t, 2H, J = 6.9 Hz), 3.08 (m, 2H), 7.54–7.93 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.45, 22.48, 22.9, 23.8, 27.8, 28.9, 31.6, 42.0, 42.9, 56.0, 128.0, 129.3, 133.6, 139.1, 210.7; EI-MS m/z 325 (M + 1, 0.4%), 324 (M^+, 2.0), 268 (0.4), 267 (4.1), 255 (3.9), 254 (25.8), 240 (1.7), 239 (13.6), 211 (6.6), 197 (18.5), 113 (100); EI-HRMS Calcd for $C_{18}H_{28}O_3S$ (M^+): 324.1759, Found: m/z 324.1759. Found: C, 66.58; H, 8.30; S, 9.94%. Calcd for $C_{18}H_{28}O_3S$: C, 66.63; H, 8.70; S, 9.88%.

To a solution of the keto sulfone (1.19 g, 3.68 mmol) in CH_2Cl_2 (24 mL) were added 1,2-bis(trimethylsilyloxy)ethane (2.69 mL, 11.0 mmol) and TMSOTf (0.0666 mL, 0.368 mmol) at 0 °C. After stirring at 0 °C for 1 h, to the mixture was added Et_3N (0.1 mL) at 0 °C. The reaction mixture was diluted with $CHCl_3$ and washed with saturated aqueous $NaHCO_3$ solution, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (60 g alumina, 1:9 EtOAc–hexane as an eluent)

to afford sulfone **4** (1.36 g, 100% for 2 steps) as a colorless syrup: $R_f = 0.30$ (1:3 EtOAc–hexane); IR (neat) 1070, 1090, 1150, 1305, 1320, 1450, 1455, 2875, 2950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J = 6.9$ Hz), 1.23–1.43 (m, 12H), 1.51–1.58 (bt, 4H, $J = 7.8$ Hz), 1.66–1.78 (m, 2H), 3.08 (m, 2H), 3.90 (m, 4H), 7.54–7.94 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.57, 22.60, 23.2, 23.8, 28.5, 29.5, 31.8, 36.6, 37.1, 56.2, 64.9, 76.6, 111.5, 128.0, 129.2, 133.6, 139.2; EI-MS *m/z* 368 (M^+, 0.1%), 325 (0.2), 285 (2.6), 284 (6.2), 283 (36.5), 157 (100); EI-HRMS Calcd for $C_{20}H_{32}O_4S$ (M^+): 368.2021, Found: *m/z* 368.2010. Found: C, 64.83; H, 8.63; S, 8.43%. Calcd for $C_{20}H_{32}O_4S$: C, 65.18; H, 8.75; S, 8.74%.

Methyl (4*S*,5*R*)-5-[(*E*,1*R*,6*R*&*S*)-1-Benzyloxy-11,11-ethylenedioxy-6-phenylsulfonylheptadec-3-en-1-yl]-4-(4-methoxybenzyloxymethyl)-2-oxooxazolidine-4-carboxylate (28). To a solution of sulfone **4** (93.5 mg, 0.254 mmol) in THF (2 mL) was added dropwise *n*-BuLi (1.59 M hexane solution, 0.239 mL, 0.381 mmol) at −78 °C, and the resulting yellow solution was stirred at −78 °C for 10 min. To this mixture was added a solution of allyl bromide **3** (46.4 mg, 0.0846 mmol) in THF (2.5 mL) dropwise via a cannula at −78 °C. The resulting solution was stirred at −78 °C for 10 min, then poured into phosphate buffer (pH 8.1, 5 mL). The products were extracted with $CHCl_3$, then dried. Removal of the solvent gave a residue, which was purified by column chromatography [5 g alumina powder (300 mesh), 1:2 to 3:1 EtOAc–hexane (gradient) as eluents] to afford a diastereomeric mixture of coupling product **28** (59.4 mg, 84%) as a colorless syrup: $R_f =$ 0.35 (1:1 EtOAc–hexane); IR (neat) 1030, 1085, 1145, 1250, 1300, 1365, 1445, 1455, 1460, 1515, 1730, 1770, 2860, 2930, 2950, 3340 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J =$ 6.6 Hz), 1.21–1.34 (m, 12H), 1.48–1.57 (m, 4H), 1.59–1.82 (m, 2H), 2.31–2.59 (m, 4H), 2.91–3.00 (m, 1H), 3.33 (s, 1.5H), 3.34 (s, 1.5H), 3.54 (d, 0.5H, $J = 8.8$ Hz), 3.57 (d, 0.5H, $J = 8.8$ Hz), 3.72–3.82 (m, 2H), 3.786 (s, 1.5H), 3.791 (s, 1.5H), 3.89 (bs, 2H), 3.90 (bs, 2H), 4.21 (d, 1H, $J = 11.9$ Hz), 4.43–4.49 (m, 3H), 4.62 (d, 0.5H, $J = 11.9$ Hz), 4.63 (d, 0.5H, $J = 11.9$ Hz), 5.38–5.59 (m, 2H), 5.67 (bs, 0.5H), 5.68 (bs, 0.5H), 6.83 (2d, 2H, $J = 8.5$ Hz), 7.14 (d, 1H, $J = 8.5$ Hz), 7.15 (d, 1H, $J = 8.5$ Hz), 7.23–7.33 (m, 5H), 7.53–7.86 (m, 5H); FAB-MS *m/z* 836 (M + H, 40.8), 794 (21.2), 793 (72.8), 792 (100); FAB-HRMS Calcd for $C_{46}H_{62}NO_{11}S$ $(M + H)^+$: 836.4044, Found: *m/z* 836.4039.

(2*S*,3*R*,4*R*)-2-Acetamido-3-acetoxy-2-acetoxymethyl-4-[(*E*)-10-oxohexadec-2-en-1-yl]-4-butanolide (30).[2d] To a solution of coupling product **28** (89.7 mg, 0.107 mmol) in THF (2 mL) was added 0.1% aqueous LiOH solution (2 mL) at 25 °C and the mixture was stirred at 25 °C for 12 h. The resulting clear yellow solution was concentrated to give crude carboxylic acid lithium salt **29**: $R_f = 0.27$ (1:9 MeOH–$CHCl_3$).

To a navy blue suspension of Li (74.3 mg, 10.7 mol) in freshly distilled liquid ammonia (2 mL, from Li) was added a solution of crude **29** in THF (2 mL) at −78 °C. After stirring at −78 °C for 30 min, to the resulting mixture was added dropwise MeOH at −78 °C until the blue color of the mixture disappeared. The reaction mixture was further stirred at 0 °C for 30 min to evaporate any excess ammonia, and then the insoluble material was removed by filtration through a pad of Celite. The Celite was rinsed with EtOAc and the filtrate was washed with 2 M aqueous HCl solution. The aqueous layer was re-extracted with EtOAc, and the combined organic layer was dried. Removal of the solvent gave a crude oxazolidinecarboxylic acid: $R_f = 0.24$ (1:2 MeOH–$CHCl_3$).

A solution of the crude oxazolidinecarboxylic acid in a mixed solvent of 2 M aqueous HCl solution and THF (1:1, 2 mL) was stirred at 25 °C for 12 h. Removal of the solvent gave a residue, which was dissolved in a mixed solvent of 10% aqueous NaOH solution and MeOH (1:3, 2 mL). After stirring at 70 °C for 8 h, the resulting mixture was concentrated and dissolved in pyridine (0.5 mL). To this solution was added Ac_2O (0.5 mL) and the mixture was stirred at 25 °C for 2 h. Removal of the solvent gave a residue, which was purified by column chromatography (2 g silica gel, 1:4 EtOAc–toluene as an eluent) to afford known 4-butanolide **30** (25.6 mg, 47%) as a colorless syrup: $R_f = 0.45$ (3:1 EtOAc–hexane) and 0.52 (1:3 MeOH–$CHCl_3$); $[\alpha]_D^{20.0}$ +53.6 (*c* 0.71, $CHCl_3$); IR (neat) 1030, 1190, 1230, 1375, 1685, 1695, 1715, 1745, 1755, 1790, 2860, 2930, 3340 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.88 (t, 3H, $J = 6.7$ Hz), 1.20–1.39 (m, 12H), 1.50–1.61 (m, 4H), 1.96–2.07 (m, 2H), 2.03 (s, 3H), 2.05 (s, 3H), 2.10 (s, 3H), 2.36–2.46 (m, 2H), 2.38 (t, 4H, $J = 7.4$ Hz), 4.52 (s, 2H), 4.72 (dt, 1H, $J = 4.4$ and 8.7 Hz), 5.39 (dt, 1H, $J = 15.2$ and 7.0 Hz), 5.57 (dt, 1H, $J = 15.2$ and 6.7 Hz), 5.80 (d, 1H, $J = 4.4$ Hz), 6.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.4, 20.6, 22.5, 22.8, 23.77, 23.83, 28.8, 28.9, 29.0, 29.1, 31.6, 32.2, 32.5, 42.75, 42.83, 62.5, 62.6, 71.9, 81.6, 123.1, 135.1, 168.9, 169.4, 170.2, 172.4, 211.7; FAB-MS *m/z* 510 (M + H, 15.8), 93 (100); FAB-HRMS Calcd for $C_{27}H_{44}NO_8$ $(M + H)^+$: 510.3067, Found: *m/z* 510.3060. The spectral data were fully identical with those reported.[1b]

(1*S*,5*R*,6*R*)-1-Hydroxymethyl-6-[(*E*)-10-oxohexadec-2-en-1-yl]-2-aza-4,7-dioxabicyclo[3.3.0]octane-3,8-dione (31). To a solution of coupling product **28** (18.9 mg, 0.0226 mmol) in THF (0.5 mL) was added 0.1% aqueous LiOH solution (0.5 mL) at 25 °C and the mixture was stirred at 25 °C for 12 h. The resulting clear solution was concentrated to give crude carboxylic acid lithium salt **29**: $R_f = 0.27$ (1:9 MeOH–$CHCl_3$).

A mixture of Li (31.3 mg, 2.26 mmol) and naphthalene (580 mg, 2.26 mmol) in THF (6 mL) was sonicated with ultrasound at 15 °C for 30 min. The resulting moss-green suspension was cooled to −18 °C. To this mixture was added a solution of the crude carboxylic acid lithium salt **29** in THF (2 mL) at −18 °C. After being stirred at −18 °C for 10 min, the reaction mixture was quenched by addition of 2 M aqueous HCl solution. The products were extracted with EtOAc, and then dried. The organic layers were concentrated and passed through a short column (1 g silica gel, 1:9 EtOAc–hexane) to remove naphthalene. Further elution (1:1 MeOH–$CHCl_3$ as an eluent) gave a mixture of hydroxy carboxylic acid and its γ-lactone. The mixture was dissolved in THF (1.5 mL) and 2 M aqueous HCl solution (0.5 mL) at 25 °C. The mixture was stirred at 25 °C for 30 min, then poured into an ice-cooled saturated aqueous $NaHCO_3$ solution. The products were extracted with $CHCl_3$, and then dried. Removal of the solvent gave a residue, which was purified with column chromatography [1 g silica gel, 1:4 to 2:3 (gradient) EtOAc–toluene as eluents] to afford bicyclic γ-lactone **31** (8.7 mg, 94%) as white crystals: $R_f =$ 0.39 (3:1 EtOAc–hexane); Mp 43.4–44.8 °C; $[\alpha]_D^{21.5}$ +3.2 (*c* 0.21, $CHCl_3$); IR (KBr) 1000, 1040, 1055, 1080, 1105, 1150, 1175, 1215, 1260, 1310, 1360, 1370, 1410, 1415, 1455, 1465, 1715, 1730, 1750, 1770, 1780, 1790, 2855, 2925, 2955, 3020, 3320 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J = 6.6$ Hz), 1.22–1.42 (m, 12H), 1.54 (m, 4H), 2.02 (dd, 2H, $J = 6.6$ and 6.6 Hz), 2.40 (t, 4H, $J = 7.5$ Hz), 2.60 (bdd, 2H, $J = 7.2$ and 7.2 Hz), 2.96–3.13 (bs, 1H), 3.93 (d, 1H, $J = 11.1$ Hz), 4.07 (d, 1H, $J =$ 11.1 Hz), 4.63 (dt, 1H, $J = 4.8$ and 7.2 Hz), 5.15 (d, 1H, $J =$ 4.8 Hz), 5.40 (dt, 1H, $J = 15.2$ and 7.2 Hz), 5.67 (dt, 1H, $J = 15.2$

and 6.6 Hz), 5.97–6.16 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.5, 23.8, 28.52, 28.54, 28.8, 28.9, 31.6, 31.76, 31.78, 32.2, 42.7, 42.9, 62.1, 66.2, 79.9, 82.0, 122.1, 136.2, 156.4, 174.5, 212.9; EI-MS *m/z* 410 (M + 1, 4.4), 409 (M^+, 18.0), 353 (2.6), 352 (10.0), 325 (2.6), 324 (14.0), 113 (77.3), 56 (100); EI-HRMS Calcd for $C_{22}H_{35}NO_6$ (M^+): 409.2464, Found: *m/z* 409.2462.

(*E*,2*S*,3*R*,4*R*)-2-Amino-3,4-dihydroxy-2-hydroxymethyl-14-oxoicos-6-enoic Acid [Myriocin (1)]. To a solution of γ-lactone **30** (14.9 mg, 0.0292 mmol) in MeOH (1 mL) was added 10% aqueous NaOH solution (1 mL) and the resulting mixture was stirred at 80 °C for 2 h. The mixture was cooled to 25 °C, then neutralized with IRC-76 resin (H^+ type). The insoluble material was removed by filtration and the filtrate was concentrated to give a residue, which was purified by column chromatography [0.9 g silica gel, 1:1:10 to 1:3:10 (gradient) H_2O–MeOH–$CHCl_3$ (lower phase) as eluents] to afford solid residue. Recrystallization (MeOH–$CHCl_3$–hexane) gave myriocin **1** (10.1 mg, 86%) as white crystals: R_f = 0.38 (1:3:10 H_2O–MeOH–$CHCl_3$, lower phase); Mp 168.4–170.1 °C; $[\alpha]_D^{24.0}$ +5.1 (*c* 0.18, MeOH); IR (KBr) 970, 1410, 1470, 1520, 1570, 1640, 1710, 2855, 2930, 3210, 3340 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 0.89 (t, 3H, *J* = 6.6 Hz), 1.21–1.39 (m, 12H), 1.52 (m, 4H, *J* = 7.0 Hz), 1.99 (dd, 2H, *J* = 6.5 and 6.5 Hz), 2.26 (dd, 2H, *J* = 6.8 and 6.8 Hz), 2.43 (t, 4H, *J* = 7.3 Hz), 3.75 (s, 1H), 3.81 (t, 1H, *J* = 6.8 Hz), 3.84 (d, 1H, *J* = 11.0 Hz), 3.98 (d, 1H, *J* = 11.0 Hz), 5.37 (dt, 1H, *J* = 14.7 and 6.8 Hz), 5.52 (dt, 1H, *J* = 14.7 and 6.5 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 14.4, 23.6, 24.9, 30.0, 30.1, 30.2, 30.4, 32.8, 33.7, 33.8, 38.7, 43.4, 43.5, 65.1, 70.3, 71.3, 73.6, 126.8, 134.7, 173.5, 214.3; FAB-MS *m/z* 402 (M + H, 70.2%), 57 (100); FAB-HRMS Calcd for $C_{21}H_{40}NO_6$ (M + H)$^+$: 402.2856, Found: *m/z* 402.2859. The spectral data were identical with those of the natural product.

Under similar conditions, γ-lactone **31** was also converted into **1** in 82% yield.

6-*O*-Benzyl-1,2-*O*-isopropylidene-3-*O*-methoxymethyl-α-D-*gluco*-hexofuranose (33). To a solution of diol **32**[29] (4.89 g, 18.5 mmol) in toluene (100 mL) was added dibutyltin oxide (4.86 g, 19.5 mmol) and the mixture was stirred under reflux for 3 h. The resulting suspension was concentrated to give a residue, which was dissolved in DMF (90 mL) at 40 °C. To this solution were added CsF (3.56 g, 23.4 mmol) and BnBr (3.47 mL, 23.4 mmol) at 40 °C and the mixture was stirred at 80 °C for 13 h. After cooling, to the reaction mixture were added 20% aqueous KF solution (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL), and the mixture was stirred at 25 °C for 1h. The products were extracted with EtOAc, and the organic layer was washed successively with water, 20% aqueous KF solution, and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (140 g silica gel, 1:4 EtOAc–toluene as an eluent) to afford benzyl ether **33** (5.78 g, 88%) as a colorless syrup: R_f = 0.57 (1:1 EtOAc–toluene); $[\alpha]_D^{26.0}$ −20.2 (*c* 1.00, $CHCl_3$); IR (neat) 1020, 1085, 1155, 1165, 1220, 1375, 1455, 2940, 2990, 3480 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.48 (s, 3H), 2.87 (d, 1H), 3.41 (s, 3H), 3.62 (dd, 1H, *J* = 5.9 and 9.8 Hz), 3.77 (dd, 1H, *J* = 2.7 and 9.8 Hz), 4.02–4.10 (m, 1H), 4.16 (dd, 1H, *J* = 2.9 and 8.8 Hz), 4.25 (d, 1H, *J* = 2.9 Hz), 4.55 (d, 1H, *J* = 3.7 Hz), 4.57 (s, 1H), 4.59 (s, 1H), 4.70 (d, 1H, *J* = 6.4 Hz), 4.75 (d, 1H, *J* = 6.4 Hz), 5.89 (d, 1H, *J* = 3.7 Hz), 7.26–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 26.8, 55.9, 67.6, 71.9, 73.4, 79.6, 80.4, 83.3, 96.7, 105.1, 111.9, 127.70, 127.73, 128.4, 138.0; EI-MS *m/z* 354 (M^+, 0.1%), 339 (0.6), 310 (3.7), 309 (20.6), 91 (100); EI-HRMS Calcd for $C_{18}H_{26}O_7$ (M^+): 354.1678, Found: *m/z* 354.1684. Found: C, 60.91; H, 7.36%. Calcd for $C_{18}H_{26}O_7$: C, 61.00; H, 7.39%.

6-*O*-Benzyl-1,2-*O*-isopropylidene-3-*O*-methoxymethyl-α-D-*xylo*-hexofuranos-5-ulose (34). A mixture of $(COCl)_2$ (2.0 M solution in CH_2Cl_2, 16.3 mL, 32.7 mmol) and DMSO (4.63 mL, 65.3 mmol) was stirred at −78 °C for 30 min. To this mixture was added a solution of alcohol **33** (5.78 g, 16.3 mmol) in CH_2Cl_2 (90 mL) at −78 °C. After being stirred at −45 °C for 1 h, the reaction mixture was quenched by addition of Et_3N (13.7 mL, 98.0 mmol). The resulting suspension was further stirred at 0 °C for 30 min, and then poured into saturated aqueous NH_4Cl solution. The products were extracted with EtOAc and the organic layer was washed with brine, and then dried. Removal of the solvent gave a residue, which was passed through a short column (100 g silica gel, 1:9 EtOAc-toluene as an eluent) to afford ketone **34** (5.75 g, 100%) as colorless syrup: R_f = 0.32 (1:5 EtOAc–toluene); $[\alpha]_D^{25.5}$ = −81.7 (*c* 1.05, $CHCl_3$); IR (neat) 1020, 1040, 1090, 1110, 1155, 1220, 1380, 1385, 1740, 2900, 2940, 2990 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.32 (s, 3H), 1.47 (s, 3H), 3.30 (s, 3H), 4.34 (d, 1H, *J* = 18.9 Hz), 4.47 (d, 1H, *J* = 18.9 Hz), 4.50 (d, 1H, *J* = 3.6 Hz), 4.55 (d, 1H, *J* = 6.9 Hz), 4.61 (d, 1H, *J* = 6.9 Hz), 4.58 (d, 1H, *J* = 3.3 Hz), 4.60 (s, 2H), 4.78 (d, 1H, *J* = 3.6 Hz), 6.00 (d, 1H, *J* = 3.3 Hz), 7.26–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 26.9, 55.9, 73.2, 74.2, 81.3, 82.3, 84.6, 96.0, 105.7, 112.5, 127.9, 128.0, 128.4, 137.2, 204.4; FAB-MS *m/z* 353 (M + H, 100%); FAB-HRMS Calcd for $C_{18}H_{24}O_7$ (M + H)$^+$: 353.1600, Found: *m/z* 353.1600. Found: C, 61.13; H, 7.07%. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.78%.

An Inseparable Mixture of Ethyl (*Z*)-4-Benzyloxy-3-{(1*R*,5*R*,7*R*,8*S*)-8-methoxymethoxy-3,3-dimethyl-2,4,6-trioxabicyclo[3.3.0]octan-7-yl}but-2-enoate and Its (*E*)-Isomer (35). To a solution of ketone **34** (5.75 g, 16.3 mmol) in toluene (85 mL) was added $Ph_3P{=}CHCO_2Et$ (8.53 g, 24.5 mmol) at 25 °C, and the mixture was stirred at 100 °C for 17 h. Removal of the solvent gave a residue, which was purified by column chromatography (200 g silica gel, 1:7 EtOAc–hexane as an eluent) to afford a geometrical mixture (*E*:*Z* = ca. 1:4) of ester **35** (6.75 g, 98%) as a colorless syrup: R_f = 0.48 (1:5 EtOAc–toluene); IR (neat) 1040, 1085, 1105, 1155, 1220, 1240, 1375, 1380, 1655, 1715, 2940, 2990 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, for the major isomer) δ 1.29 (t, 3H, *J* = 7.6 Hz), 1.32 (s, 3H), 1.52 (s, 3H), 3.26 (s, 3H), 4.19 (m, 2H), 4.33–4.36 (m, 2H), 4.50 (d, 1H, *J* = 6.6 Hz), 4.54 (d, 1H, *J* = 3.6 Hz), 4.571 (d, 1H, *J* = 6.6 Hz), 4.574 (s, 2H), 4.61 (d, 1H, *J* = 3.6 Hz), 5.86–5.89 (m, 1H), 5.91 (d, 1H, *J* = 3.6 Hz), 6.22 (dd, 1H, *J* = 1.8 and 3.6 Hz), 7.26–7.35 (m, 5H); EI-MS *m/z* 423 (M + 1, 1.7%), 422 (M^+, 5.6), 408 (4.1), 407 (16.4), 391 (1.8), 378 (2.8), 377 (10.2), 362 (2.0), 361 (10.6), 360 (42.9), 333 (6.6), 332 (21.7), 331 (100); EI-HRMS Calcd for $C_{22}H_{30}O_8$ (M^+): 422.1941, Found: *m/z* 422.1937. Found: C, 62.37; H, 7.29%. Calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16%.

(*Z*)-4-Benzyloxy-3-{(1*R*,5*R*,7*R*,8*S*)-8-methoxymethoxy-3,3-dimethyl-2,4,6-trioxabicyclo[3.3.0]oct-7-yl}but-2-en-1-ol (36*Z*) and Its (*E*)-Isomer (36*E*). To a solution of a mixture (ca. 4:1) of ester **35** (20.0 g, 44.5 mmol) in toluene (300 mL) was added dropwise DIBAL-H (1.5 M solution in toluene, 59.3 mL, 88.9 mmol) at −78 °C. After being stirred at −78 °C for 3 h, the reaction mixture was quenched by addition of MeOH. The mixture was diluted with Et_2O and washed with 1 M aqueous HCl solution. The aqueous layer was extracted with Et_2O. The combined organic layer was washed successively with saturated aqueous

$NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (300 g silica gel, 1:5 EtOAc–toluene as an eluent) to afford *Z*-allylic alcohol **36*Z*** (13.1 g, 73%) first as a colorless syrup: R_f = 0.35 (1:1 EtOAc–hexane); $[\alpha]_D^{24.5}$ −46.9 (*c* 1.02, $CHCl_3$); IR (neat) 1030, 1085, 1150, 1165, 1215, 1375, 1385, 1455, 2890, 2935, 2990, 3450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.51 (s, 3H), 2.14 (bs, 1H), 3.30 (s, 3H), 4.05 (s, 2H), 4.18 (d, 1H, J = 2.9 Hz), 4.22 (dd, 1H, J = 7.1 and 12.7 Hz), 4.30 (dd, 1H, J = 7.1 and 12.7 Hz), 4.48–4.63 (m, 5H), 4.98 (m, 1H), 5.94 (d, 1H, J = 3.7 Hz), 6.04 (bt, 1H, J = 7.1 Hz), 7.26–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 26.8, 55.9, 58.4, 72.2, 72.3, 79.6, 81.7, 83.2, 96.1, 104.3, 111.8, 127.6 (2C), 128.4, 129.7, 133.5, 138.2; FAB-MS *m/z* 381 (M + H, 100); FAB-HRMS Calcd for $C_{20}H_{29}O_7$ $(M + H)^+$: 381.1913, Found: *m/z* 381.1916. Found: C, 62.84; H, 7.61%. Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42%.

Further elution gave *E*-isomer **36*E*** (3.23 g, 18%) as a yellow syrup: R_f = 0.26 (1:1 EtOAc-hexane); $[\alpha]_D^{24.5}$ −44.7 (*c* 1.02, $CHCl_3$); IR (neat) 1030, 1080, 1150, 1165, 1215, 1375, 1385, 1455, 2860, 2930, 2990, 3440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.51 (s, 3H), 1.76 (bs, 1H), 3.29 (s, 3H), 4.07–4.27 (m, 3H), 4.21 (d, 2H, J = 6.6 Hz), 4.47–4.60 (m, 5H), 4.78 (m, 1H), 5.89 (d, 1H, J = 3.7 Hz), 6.11 (bt, 1H, J = 6.6 Hz), 7.27–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 27.0, 56.0, 59.0, 66.2, 72.8, 81.4, 81.6, 83.7, 96.3, 104.7, 112.0, 128.0 (2C), 128.7, 131.0, 134.1, 137.9; FAB-MS *m/z* 381 (M + H, 32.9), 241 (100); FAB-HRMS Calcd for $C_{20}H_{29}O_7$ $(M + H)^+$: 381.1913, Found: *m/z* 381.1917. Found: C, 62.84; H, 7.68%. Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42%.

N*-[(*R*)-1-Benzyloxy-2-{(1*R*,5*R*,7*R*,8*S*)-3,3-dimethyl-8-methoxymethoxy-2,4,6-trioxabicyclo[3.3.0]octan-7-yl}but-3-en-2-yl]trichloroacetamide (37*R*) and Its (*S*)-Buten-2-yl Isomer (37*S*).** To a solution of allylic alcohol **36*Z (102 mg, 0.268 mmol) in CH_2Cl_2 (2 mL) were added trichloroacetonitrile (0.0537 mL, 0.535mol) and DBU (0.008 mL, 0.0535mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. Removal of the solvent gave a residue, which was passed through a short column chromatography (1 g silica gel, 1:4 EtOAc–hexane containing 1 vol% Et_3N as an eluent) to afford trichloroacetimidate (139 mg) as a yellow syrup, which was used for the next reaction without further purification: R_f = 0.48 (1:2 EtOAc–hexane).

To a solution of the crude imidate (139 mg, 0.265 mmol) in *o*-xylene (14 mL) was added solid K_2CO_3 (40 mg), and the mixture was heated at 140 °C for 156 h in a sealed tube under Ar atmosphere. Removal of the solvent gave a residue, which was purified by PLC (1:49 EtOAc–toluene as an eluent) to afford **37*S*** (19.4 mg, 14%) as a pale yellow syrup: R_f = 0.59 (1:10 EtOAc–toluene); $[\alpha]_D^{29.0}$ −8.9 (*c* 1.02, $CHCl_3$); IR (neat) 1030, 1090, 1160, 1215, 1520, 1725, 2890, 2940, 2990, 3350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.46 (s, 3H), 3.38 (s, 3H), 3.85 (d, 1H, J = 8.5 Hz), 4.46 (d, 1H, J = 8.5 Hz), 4.17 (d, 1H, J = 2.6 Hz), 4.59 (s, 2H), 4.64 (d, 1H, J = 3.3 Hz), 4.64 (d, 1H, J = 7.1 Hz), 4.71 (d, 1H, J = 7.1 Hz), 4.72 (d, 1H, J = 2.6 Hz), 5.35 (d, 1H, J = 11.0 Hz), 5.42 (d, 1H, J = 17.9 Hz), 5.97 (d, 1H, J = 3.3 Hz), 6.11 (dd, 1H, J = 11.0 and 17.9 Hz), 7.26–7.34 (m, 5H), 8.27 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 26.7, 56.3, 61.5, 70.1, 73.9, 80.8, 82.6, 82.8, 93.3, 97.2, 103.8, 112.0, 115.8, 128.0, 128.1, 128.4, 135.6, 137.4, 160.4; EI-MS *m/z* 527 (M + 4, 2.0%), 526 (M + 3, 1.8), 525 (M + 2, 2.8), 524 (M + 1, 1.8), 523 (M^+, 2.8), 512 (4.0), 511 (2.7), 510 (10.6), 509 (2.4), 508 (10.2), 407 (4.1), 406 (17.8), 405 (8.4), 404 (40.5), 403 (8.9), 402 (42.7), 364 (2.6), 363 (27.3), 362 (100); EI-HRMS Calcd for $C_{22}H_{28}{}^{35}Cl_3NO_7$ (M^+): 523.0931, Found: *m/z* 523.0931. Found: C, 50.54; H, 5.44; N, 2.47%. Calcd for $C_{22}H_{28}Cl_3NO_7$: C, 50.35; H, 5.38; N, 2.67%.

Further elution gave *R*-isomer **37*R*** (89.4 mg, 64%) as a pale yellow syrup: R_f = 0.56 (1:10 EtOAc–toluene); $[\alpha]_D^{29.0}$ ~0.0 (*c* 1.00, $CHCl_3$); IR (neat) 1030, 1090, 1160, 1215, 1520, 1720, 2895, 2940, 2990, 3360, 3405 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.49 (s, 3H), 3.26 (s, 3H), 3.97 (d, 1H, J = 9.6 Hz), 4.04 (d, 1H, J = 9.6 Hz), 4.25 (s, 2H), 4.36 (d, 1H, J = 6.8 Hz), 4.485 (d, 1H, J = 6.8 Hz), 4.490 (d, 1H, J = 9.6 Hz), 4.57 (d, 1H, J = 9.6 Hz), 4.58 (d, 1H, J = 3.9 Hz), 5.31 (d, 1H, J = 17.6 Hz), 5.32 (d, 1H, J = 11.0 Hz), 5.90 (d, 1H, J = 3.9 Hz), 6.12 (dd, 1H, J = 11.0 and 17.6 Hz), 7.27-7.38 (m, 5H), 8.27 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 26.7, 56.5, 62.2, 70.4, 73.3, 77.4, 82.3, 82.4, 93.4, 96.9, 104.4, 112.2, 116.4, 127.37, 127.44, 128.2, 128.4, 133.7, 138.1, 160.4; EI-MS *m/z* 527 (M + 4, 2.7%), 526 (M + 3, 2.4), 525 (M + 2, 5.9), 524 (M + 1, 2.3), 523 (M^+, 4.7), 513 (2.2), 512 (6.3), 511 (5.1), 510 (14.0), 509 (4.1), 508 (14.7), 407 (4.1), 406 (20.9), 405 (9.9), 404 (46.6), 403 (10.1), 402 (44.4), 364 (5.1), 363 (30.8), 362 (100); EI-HRMS Calcd for $C_{22}H_{28}{}^{35}Cl_3NO_7$ (M^+): 523.0931, Found: *m/z* 523.0931. Found: C, 50.57; H, 5.49; N, 2.58%. Calcd for $C_{22}H_{28}Cl_3NO_7$: C, 50.35; H, 5.38; N, 2.67%.

Overman rearrangement of *E*-allylic imidate derived from allylic alcohol **36*E*** was carried out by the same procedure, and gave the rearranged products **37*R*** and **37*S*** in 12 and 45% yields, respectively.

N*-[(*R*)-1-Benzyloxy-2-{(1*R*,5*R*,7*R*,8*S*)-3,3-dimethyl-8-methoxymethoxy-2,4,6-trioxabicyclo[3.3.0]octan-7-yl}-3-hydroxyprop-2-yl]trichloroacetamide (38).** Ozone was introduced into a solution of compound **37*R (1.13 g, 2.15 mmol) in CH_2Cl_2 (20 mL) at −78 °C for 20 min. After the complete consumption of the starting material was confirmed (TLC analysis), excess ozone was removed with a stream of argon gas. To this mixture was added Me_2S (2.20 mL, 29.5 mmol) at −78 °C, and the resulting mixture was further stirred at 0 °C for 2.5 h. Removal of the solvent gave a residue, which was purified by column chromatography (50 g silica gel, 1:4 EtOAc–hexane as an eluent) to afford aldehyde: R_f = 0.33 (1:3 EtOAc–hexane); IR (neat) 1025, 1090, 1160, 1215, 1375, 1385, 1505, 1715, 1730, 2890, 2940, 2990, 3355 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.50 (s, 3H), 3.32 (s, 3H), 4.15 (d, 1H, J = 3.3 Hz), 4.16 (d, 1H, J = 10.2 Hz), 4.31 (d, 1H, J = 10.2 Hz), 4.46 (d, 1H, J = 12.3 Hz), 4.48 (d, 1H, J = 6.6 Hz), 4.51 (d, 1H, J = 6.6 Hz), 4.53 (d, 1H, J = 12.3 Hz), 4.54 (d, 1H, J = 3.3 Hz), 4.98 (d, 1H, J = 3.6 Hz), 5.91 (d, 1H, J = 3.6 Hz), 7.18-7.38 (m, 5H), 8.29 (s, 1H), 9.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 26.8, 56.5, 66.2, 66.4, 73.6, 79.6, 80.9, 82.2, 92.1, 96.7, 104.9, 112.6, 127.6, 127.9, 128.4, 137.2, 161.4, 195.3; EI-MS *m/z* 529 (M + 4, 1.2%), 528 (M + 3, 1.4), 527 (M + 2, 2.8), 526 (M + 1, 1.0), 525 (M^+, 2.7), 514 (1.6), 512 (3.8), 510 (3.8), 499 (4.3), 498 (5.0), 497 (11.0), 496 (7.5), 495 (10.6), 438 (8.1), 437 (4.5), 436 (12.2), 435 (6.3), 434 (12.3), 408 (8.3), 407 (4.4), 406 (16.0), 405 (4.5), 404 (17.6), 308 (32.5), 307 (14.0), 306 (97.5), 305 (19.9), 304 (100); EI-HRMS Calcd for $C_{21}H_{28}Cl_3NO_8$ (M^+): 525.0723, Found: *m/z* 525.0724.

At 0 °C, to a solution of the aldehyde in Et_2O (30 mL) was added dropwise $Zn(BH_4)_2$[19] (0.184 M solution in Et_2O, 11.7 mL, 2.15 mmol). After being stirred at 25 °C for 1 h, the reaction mixture was quenched by addition of H_2O, then diluted with EtOAc, and washed successively with 1 M aqueous HCl solution and brine, and then dried. Removal of the solvent gave a residue, which was

purified by column chromatography (50 g silica gel, 1:2 EtOAc–toluene as an eluent) to afford alcohol **38** (1.05 g, 93%) as a colorless syrup: R_f = 0.30 (1:2 EtOAc–hexane); $[\alpha]_D^{28.5}$ −7.7 (*c* 1.00, $CHCl_3$); IR (neat) 1025, 1065, 1085, 1100, 1160, 1215, 1260, 1375, 1385, 1455, 1530, 1715, 2890, 2940, 2990, 3330, 3350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.49 (s, 3H), 3.28 (s, 3H), 3.90 (s, 2H), 3.92 (d, 1H, *J* = 12.5 Hz), 4.25 (d, 1H, *J* = 12.5 Hz), 4.29 (m, 2H), 4.40–4.62 (m, 5H), 5.89 (d, 1H, *J* = 3.7 Hz), 7.26–7.35 (m, 5H), 8.66 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 26.8, 56.4, 63.0, 65.2, 69.3, 73.9, 79.8, 82.4, 84.0, 93.1, 97.1, 103.9, 112.1, 128.06, 128.11, 128.5, 137.3, 162.2; EI-MS *m/z* 529 (M + 2, 0.2%), 527 (M^+, 0.2), 514 (0.2), 512 (0.2), 498 (0.5), 496 (0.5), 378 (2.5), 376 (2.4), 228 (4.9), 91 (100); EI-HRMS Calcd for $C_{21}H_{28}{}^{35}Cl_3NO_8$ (M^+): 527.0880, Found: *m/z* 527.0882. Found: C, 47.83; H, 5.56; N, 2.45%. Calcd for $C_{21}H_{28}Cl_3NO_8$: C, 47.70; H, 5.34; N, 2.65%.

(2*S*,3*R*,4*S*,5*R*,6*S*)-2,3,5-Triacetoxy-6-benzyloxymethyl-4-methoxymethoxy-8-oxa-1-azabicyclo[4.3.0]nonan-9-one (39). To a solution of alcohol **38** (161 mg, 0.304 mmol) in CH_2Cl_2 (3.2 mL) was added DBU (0.0044 mL, 0.0304 mmol) and the mixture was stirred at 25 °C for 29 h. Removal of the solvent gave a residue, which was purified by column chromatography (4 g silica gel, 1:1 EtOAc–hexane as an eluent) to afford oxazolidinone (123 mg, 98%) as a colorless syrup: R_f = 0.18 (1:1 EtOAc–hexane); $[\alpha]_D^{28.5}$ −8.8 (*c* 1.12, $CHCl_3$); IR (neat) 1035, 1085, 1160, 1215, 1260, 1375, 1385, 1455, 1475, 1760, 2870, 2940, 2990, 3320 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.49 (s, 3H), 3.29 (s, 3H), 3.47 (d, 1H, *J* = 9.0 Hz), 3.51 (d, 1H, *J* = 9.0 Hz), 4.04 (d, 1H, *J* = 3.2 Hz), 4.28 (d, 1H, *J* = 3.2 Hz), 4.29 (d, 1H, *J* = 8.5 Hz), 4.44 (d, 1H, *J* = 6.8 Hz), 4.47 (d, 1H, *J* = 11.9 Hz), 4.51 (d, 1H, *J* = 8.5 Hz), 4.58 (m, 1H), 4.59 (d, 1H, *J* = 6.8 Hz), 4.60 (d, 1H, *J* = 11.9 Hz), 5.69 (bs, 1H), 5.93 (d, 1H, *J* = 3.7 Hz), 7.28–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 26.8, 56.6, 60.3, 71.4, 72.6, 73.7, 78.7, 81.9, 82.9, 96.6, 104.4, 111.8, 128.0, 128.2, 128.6, 137.0, 159.2; EI-MS *m/z* 410 (M + 1, 5.7), 409 (M^+, 15.5), 395 (8.0), 394 (39.7), 379 (3.2), 378 (14.8), 366 (3.7), 365 (12.1), 364 (58.2), 320 (2.2), 319 (12.3), 318 (55.8), 290 (9.5), 289 (50.9), 288 (100).

A solution of the oxazolidinone (123 mg, 0.300 mmol) in TFA and H_2O (1:1, 3 mL) was stirred at 0 °C for 18 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc, and then dried. Removal of the solvent gave a residue, which was dissolved in a mixed solvent of pyridine (0.5 mL) and Ac_2O (0.5 mL). After being stirred at 25 °C for 7 h, the reaction mixture was concentrated to give a residue, which was purified by column chromatography (1.5 g silica gel, 1:3 EtOAc–toluene as an eluent) to afford triacetate **39** (57.9 mg, 38% from **38**) as white crystals: R_f = 0.54 (1:1 EtOAc–toluene); Mp 154.7–157.2 °C; $[\alpha]_D^{21.5}$ +7.9 (*c* 0.94, $CHCl_3$); IR (KBr) 1040, 1110, 1225, 1370, 1410, 1745, 1755, 1770, 1780, 2895, 2930, 2940, 3030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.06 (s, 3H), 2.09 (s, 3H), 3.38 (s, 3H), 3.62 (d, 1H, *J* = 9.0 Hz), 3.97 (dd, 1H, *J* = 2.7 and 2.7 Hz), 4.06 (d, 1H, *J* = 9.0 Hz), 4.21 (d, 1H, *J* = 9.3 Hz), 4.30 (d, 1H, *J* = 9.3 Hz), 4.52 (d, 1H, *J* = 11.7 Hz), 4.56 (d, 1H, *J* = 11.7 Hz), 4.63 (d, 1H, *J* = 6.6 Hz), 4.70 (d, 1H, *J* = 6.6 Hz), 5.05 (dd, 1H, *J* = 2.7 Hz), 5.14 (d, 1H, *J* = 2.7 Hz), 6.41 (bs, 1H), 7.23–7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.88, 20.93, 21.1, 56.2, 60.2, 66.9, 67.8, 68.9, 71.3, 71.7, 73.8, 75.3, 96.4, 127.9, 128.3, 128.7, 137.2, 155.9, 168.3, 169.2, 169.7; FAB-MS *m/z* 496 (M + H, 1.1%), 459 (1.2), 304 (4.9), 437 (6.5), 436 (37.3), 277 (100); FAB-HRMS Calcd for $C_{23}H_{30}NO_{11}$ $(M + H)^+$: 496.1819, Found: *m/z* 496.1814. Found: C, 55.71; H, 5.72; N, 2.80%. Calcd for $C_{23}H_{29}NO_{11}$: C, 55.75; H, 5.90; N, 2.83%.

Ethyl (*E*,4*S*,5*R*,6*R*,7*S*)-7-Benzyloxymethyl-4,5:6,8-bis(isopropylidenedioxy)-7-(trichloroacetamido)oct-2-enoate (42). To a solution of alcohol **38** (955 mg, 1.81 mmol) in THF (20 mL) was added dropwise 12 M aqueous HCl solution (10 mL) at 0 °C, and the mixture was stirred at 25 °C for 3 h. The products were extracted with $CHCl_3$, and then dried. Removal of the solvent gave a residue, which was passed through a short column (20 g silica gel, 1:15 MeOH–$CHCl_3$ as an eluent) to give crude lactol **40** as a pale yellow syrup: R_f = 0.23 (1:8 MeOH–$CHCl_3$).

To a solution of the lactol **40** in CH_2Cl_2 (16 mL) were added $Ph_3P{=}CHCO_2Et$ (1.89 g, 5.42 mmol) and benzoic acid (22.2 mg, 0.181 mmol) at 25 °C, and the mixture was stirred at 25 °C for 2.5 h. Removal of the solvent gave a residue, which was passed through a short column (20 g silica gel, 1:2 EtOAc–toluene as an eluent) to afford crude tetrol **41** as a yellow syrup: R_f = 0.47 (2:1 EtOAc–toluene).

To a solution of the tetrol **41** in a mixed solvent of benzene (5 mL) and 2,2-dimethoxypropane (15 mL) was added CSA until the pH value of the solution became lower than 4.0. After being stirred at 50 °C for 13 h, the reaction mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (50 g silica gel, 1:10 EtOAc–hexane as an eluent) to afford ester **42** (641 mg, 46% for 3 steps) as a colorless syrup: R_f = 0.60 (1:5 EtOAc–toluene); $[\alpha]_D^{24.0}$ +20.1 (*c* 0.82, $CHCl_3$); IR (neat) 1085, 1160, 1240, 1305, 1370, 1385, 1455, 1540, 1665, 1715, 1730, 2870, 2905, 2940, 2990, 3340 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 3H, *J* = 7.1 Hz), 1.38 (s, 3H), 1.42 (s, 3H), 1.43 (s, 3H), 1.46 (s, 3H), 3.67 (d, 1H, *J* = 9.7 Hz), 3.87 (d, 1H, *J* = 9.7 Hz), 3.96 (d, 1H, *J* = 12.2 Hz), 4.03 (d, 1H, *J* = 8.3 Hz), 4.09 (s, 1H), 4.25 (q, 2H, *J* = 7.1 Hz), 4.39 (d, 1H, *J* = 11.9 Hz), 4.53 (d, 1H, *J* = 12.2 Hz), 4.54 (d, 1H, *J* = 11.9 Hz), 4.69 (ddd, 1H, *J* = 1.0, 6.1 and 8.3 Hz), 6.10 (dd, 1H, *J* = 1.0 and 15.6 Hz), 6.87 (dd, 1H, *J* = 6.1 and 15.6 Hz), 7.20-7.38 (m, 5H), 8.50 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 19.4, 26.1, 27.1, 28.3, 57.8, 60.8, 61.5, 67.2, 68.0, 73.6, 75.6, 78.7, 93.2, 96.1, 99.6, 111.2, 123.5, 127.8, 128.0, 128.5, 137.2, 142.9, 161.4, 165.6; EI-MS *m/z* 582 (M − CH_3 + 2, 2.7%), 580 (M − CH_3 + 1, 6.5), 578 (M − CH_3, 6.5), 522 (4.9), 520 (4.8), 502 (2.9), 501 (5.1), 500 (3.9), 499 (6.3), 170 (100); EI-HRMS Calcd for $C_{25}H_{31}{}^{35}Cl_3NO_8$ (M − CH_3): 578.1114, Found: *m/z* 578.1119. Found: C, 52.67; H, 5.55; N, 2.22%. Calcd for $C_{26}H_{34}Cl_3NO_8$: C, 52.49; H, 5.76; N, 2.35%.

***tert*-Butyl *N*-[(*E*,2*S*,3*R*,4*R*,5*S*)-2-Benzyloxymethyl-8-hydroxy-1,3:4,5-bis(isopropylidenedioxy)oct-6-ene-2-yl]carbamate (43).** To a solution of DIBAL-H (1.01 M in toluene, 2.99 mL, 3.02 mmol) in toluene (3 mL) was added a solution of ester **42** (359 mg, 0.603 mmol) in toluene (12 mL) dropwise via a cannula at −78 °C. The mixture was stirred at −78 °C for 4 h, and then quenched by slow addition of cooled acetone. To the resulting solution was added solid $Na_2SO_4{\cdot}10H_2O$ (large excess) at 0 °C. After stirring for 1 h at 25 °C, the insoluble materials were filtered off and the filtrate was concentrated to give crude amine: R_f = 0.54 (1:8 MeOH–$CHCl_3$).

To a solution of the crude amine in MeOH (6 mL) were added $NaHCO_3$ (63.4 mg, 0.754 mmol) and Boc_2O (0.523 mL, 2.37 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h, and then diluted with EtOAc. The organic layer was washed

successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (5 g silica gel, 1:3 EtOAc–toluene as an eluent) to afford *tert*-butyl carbamate **43** (223 mg, 90%) as a colorless syrup: R_f = 0.55 (1:8 MeOH–$CHCl_3$); $[\alpha]_D^{24.0}$ +1.9 (*c* 0.74, $CHCl_3$); IR (neat) 1075, 1160, 1250, 1370, 1385, 1455, 1505, 1515, 1520, 1685, 1715, 2870, 2940, 2995, 3405, 3460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (bs, 21H), 1.62 (bs, 1H), 3.74 (d, 1H, J = 9.8 Hz), 3.85 (d, 1H, J = 9.8 Hz), 3.92 (d, 1H, J = 11.9 Hz), 3.96 (s, 1H), 3.99 (d, 1H, J = 8.5 Hz), 4.10 (bt, 2H, J = 4.9 Hz), 4.34 (d, 1H, J = 11.9 Hz), 4.41–4.50 (m, 3H), 5.60 (dd, 1H, J = 8.0 and 15.6 Hz), 5.92 (dt, 1H, J = 15.6 and 4.9 Hz), 6.18 (bs, 1H), 7.22–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 26.1, 27.4, 27.5, 28.4, 56.0, 62.6, 63.4, 67.2, 70.4, 73.4, 77.5, 78.8, 78.9, 96.1, 99.5, 110.2, 127.4, 127.7, 128.4, 134.9, 138.1, 155.3; FAB-MS *m/z* 530 (M + Na, 9.1%), 508 (M + H, 100%); FAB-HRMS Calcd for $C_{27}H_{42}NO_8$ $(M + H)^+$: 508.2910, Found: *m/z* 508.2912. Found: C, 63.98; H, 8.10; N, 2.61%. Calcd for $C_{27}H_{41}NO_8$: C, 63.88; H, 8.14; N, 2.76%.

***tert*-Butyl *N*-[(*E*,2*S*,3*R*,4*R*,5*S*)-2-Benzyloxymethyl-8-bromo-1,3:4,5-bis(isopropylidenedioxy)oct-6-ene-2-yl]carbamate (44).** To a solution of allylic alcohol **43** (71.4 mg, 0.141 mmol) in CH_2Cl_2 (2.2 mL) was added Et_3N (0.0492 mL, 0.353 mmol) at 0 °C. After stirring at 0 °C for 5 min, to this solution was added MsCl (0.0273 mL, 0.353 mmol) at 0 °C. The resulting mixture was stirred at 25 °C for 20 min and then diluted with EtOAc. The organic layer was washed successively with 1 M aqueous HCl solution, saturated $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a crude mesylate: R_f = 0.34 (1:3 EtOAc–toluene).

To a solution of the crude mesylate in THF (2.2 mL) was added LiBr (120 mg, 1.41 mmol) at 25 °C. After being stirred at 25 °C for 40 min, the mixture was diluted with EtOAc and washed with H_2O. Removal of the solvent gave a residue, which was purified by column chromatography (3.5 g silica gel, 1:7 EtOAc–hexane as an eluent) to afford allyl bromide **44** (72.2 mg, 90%) as a colorless syrup: R_f = 0.76 (1:3 EtOAc–toluene); $[\alpha]_D^{22.5}$ +5.8 (*c* 1.25, $CHCl_3$); IR (neat) 1070, 1125, 1170, 1205, 1250, 1365, 1385, 1455, 1505, 1515, 1715, 2870, 2940, 2990, 3410 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40–1.44 (bs, 21H), 3.74 (d, 1H, J = 9.8 Hz), 3.83 (d, 1H, J = 9.8 Hz), 3.86–3.90 (m, 3H), 3.94 (s, 1H), 3.98 (d, 1H, J = 8.5 Hz), 4.33 (d, 1H, J = 11.9 Hz), 4.42 (d, 1H, J = 11.9 Hz), 4.45 (dd, 1H, J = 7.6, and 8.5 Hz), 4.51 (d, 1H, J = 11.9 Hz), 5.56 (dd, 1H, J = 7.6 and 15.1 Hz), 5.97 (dt, 1H, J = 15.1 and 7.3 Hz), 6.16 (bs, 1H), 7.24–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 26.1, 27.3, 27.4, 28.4, 30.9, 56.1, 63.4, 67.3, 70.3, 73.4, 76.9, 78.8, 78.9, 99.5, 110.4, 127.5, 127.7, 128.4, 131.1, 131.3, 138.0, 155.3; FAB-MS *m/z* 572 (M + 3, 100%), 570 (M + H, 91.3); FAB-HRMS Calcd for $C_{27}H_{41}{}^{81}BrNO_7$ $(M + H)^+$: 572.2046, Found: *m/z* 572.2059.

***tert*-Butyl *N*-[(*E*,2*S*,3*R*,4*R*,5*S*,9*R*&*S*)-2-Benzyloxymethyl-14,14-ethylenedioxy-1,3:4,5-bis(isopropylidenedioxy)-9-phenylsulfonylicos-6-ene-2-yl]carbamate (45).** To a solution of sulfone **4** (93.6 mg, 0.254 mmol) in THF (1 mL) was added *n*-BuLi (1.59 M hexane solution, 0.447 mL, 0.710 mmol) at −78 °C and the resulting yellow solution was stirred at −78 °C for 10 min. To the mixture was added a solution of allyl bromide **43** (72.2 mg, 0.127 mmol) in THF (1 mL) dropwise via a cannula at −78 °C. The resulting yellow solution was stirred at −78 °C for 15 min, and then poured into phosphate buffer (pH 8.1, 5 mL). The products were extracted with EtOAc, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (4 g alumina, 1:9 EtOAc–hexane as an eluent) to afford a diastereomeric mixture of coupling product **45** (91.3 mg, 85%) as a colorless syrup: R_f = 0.45 (1:3 EtOAc–toluene, 3 times); IR (neat) 1075, 1150, 1160, 1250, 1305, 1365, 1380, 1455, 1505, 1520, 1715, 2870, 2930, 3405 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 6.6 Hz), 1.15–1.92 (m, 39H), 2.25–2.66 (m, 2H), 2.95 (m, 1H), 3.71–4.23 (m, 9H), 4.29–4.56 (m, 4H), 5.38–5.52 (m, 1H), 5.69–5.85 (m, 1H), 6.19 (s, 1H), 7.20–7.37 (m, 5H), 7.49–7.99 (m, 5H); FAB-MS *m/z* 858 (M + H, 19.3%), 680 (100); FAB-HRMS Calcd for $C_{47}H_{72}NO_{11}S$ $(M + H)^+$: 858.4826, Found: *m/z* 858.4819.

***tert*-Butyl *N*-[(*E*,2*S*,3*R*,4*R*,5*S*)-14,14-Ethylenedioxy-2-hydroxymethyl-1,3:4,5-bis(isopropylidenedioxy)icos-6-ene-2-yl]carbamate (46).** A mixture of Li (22.3 mg, 3.22 mmol) and naphthalene (412 mg, 3.22 mmol) in THF (1 mL) was sonicated with ultrasound at 15 °C for 30 min. The resulting moss-green suspension was cooled to −18 °C. To this mixture was added a solution of coupling product **45** (27.6 mg, 0.0322 mmol) in THF (1 mL) at −18 °C via a cannula. The reaction mixture was stirred at −18 °C for 10 min, and then quenched by addition of H_2O until the green color of the mixture disappeared. The products were extracted with EtOAc, and then dried. Removal of the solvent gave a residue, which was chromatographed on a short column (2.5 g silica gel, 1:19 EtOAc–hexane) to remove naphthalene. Further elution (1:6 EtOAc–hexane as an eluent) provided alcohol **46** (10.5 mg, 52%) as colorless syrup: R_f = 0.57 (1:2 EtOAc–hexane); $[\alpha]_D^{24.0}$ +2.9 (*c* 0.45, $CHCl_3$); IR (neat) 1050, 1065, 1170, 1250, 1365, 1380, 1455, 1505, 1520, 1695, 1715, 2860, 2930, 2985, 3410, 3480 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 6.7 Hz), 1.23-1.37 (m, 16H), 1.40 (s, 6H), 1.44 (s, 6H), 1.45 (s, 9H), 1.53–1.63 (m, 4H), 2.06 (dd, 2H, J = 6.8 and 6.8 Hz), 3.54–3.61 (m, 1H), 3.58 (s, 1H), 3.71 (d, 1H, J = 8.3 Hz), 3.77 (d, 1H, J = 12.5 Hz), 3.87–3.94 (m, 1H), 3.92 (s, 4H), 4.22 (d, 1H, J = 12.5 Hz), 4.37 (dd, 1H, J = 8.3 and 8.3 Hz), 4.43 (bdd, 1H, J = 3.4 and 9.0 Hz), 5.40 (dd, 1H, J = 8.3 and 15.3 Hz), 5.76 (dt, 1H, J = 15.3 and 6.8 Hz), 6.07 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 17.5, 19.1, 22.6, 23.7, 23.8, 26.1, 27.4, 28.3, 28.4, 28.8, 29.0, 29.59, 29.64, 31.8, 32.2, 37.1, 37.2, 56.4, 63.5, 64.9, 65.9, 69.2, 77.2, 78.4, 78.9, 79.8, 99.2, 99.9, 109.8, 111.9, 126.3, 138.0, 157.1; FAB-MS *m/z* 628 (M + H, 100%); FAB-HRMS Calcd for $C_{34}H_{62}NO_9$ $(M + H)^+$: 628.4424, Found: *m/z* 628.4402.

(2*S*,3*R*,4*R*)-2-Acetamido-3-acetoxy-2-acetoxymethyl-4-[(*E*,*S*)-1-acetoxy-10-oxohexadec-2-en-1-yl)-4-butanolide (48). A solution of $(COCl)_2$ (2.0 M solution in CH_2Cl_2, 0.179 mL, 0.358 mmol) and DMSO (0.0509 mL, 0.717 mmol) was stirred at −78 °C for 30 min. To this mixture was added a solution of alcohol **46** (10.5 mg, 0.0163 mmol) in CH_2Cl_2 (1 mL) at −78 °C. After stirring at a temperature under −45 °C for 2 h, to the reaction mixture was added Et_3N (0.145 mL, 1.08 mmol) at 0 °C. The resulting suspension was further stirred at 0 °C for 30 min, and then diluted with EtOAc. The organic layer was washed with brine, and then dried. Removal of the solvent gave a residue, which was passed through a column chromatograph (1 g silica gel, 1:19 EtOAc–toluene as an eluent) to afford crude aldehyde, which was used for the next reaction without further purification: R_f = 0.57 (1:3 EtOAc–hexane).

To a solution of the crude aldehyde in a mixed solvent of *t*-BuOH and H_2O (1:1, 0.5 mL) were added successively $NaH_2PO_4 \cdot 2H_2O$ (7.5 mg, 0.048 mmol), $HOSO_2NH_2$ (7.0 mg,

0.072 mmol) and $NaClO_2$ (6.5 mg, 0.072 mmol) at 25 °C. After being stirred at 25 °C for 15 min, to the mixture was added 20 wt% aqueous $Na_2S_2O_3$ solution until yellow color of the mixture disappeared. The products were extracted with $CHCl_3$, and then dried. Removal of the solvent afforded a crude carboxylic acid **47** as a colorless oil, which was used for the next reaction without further purification: $R_f = 0.58$ (1:6 MeOH–$CHCl_3$).

To a solution of carboxylic acid **47** in THF (0.2 mL) was added TFA (0.4 mL) at 25 °C, and the mixture was stirred at 25 °C for 1 h. To the resulting pale yellow solution was added H_2O (0.2 mL) at 25 °C, and the mixture was further stirred at 50 °C for 2.5 h. Removal of the solvent gave a residue, which was diluted with MeOH. Then the pH of the solution was made basic by addition of K_2CO_3. Insoluble materials were filtered off, and then the filtrate was concentrated to give a residue, which was dissolved with a mixed solvent of pyridine (0.3 mL) and Ac_2O (0.3 mL) at 25 °C. After being stirred at 25 °C for 2 h, the mixture was diluted with EtOAc and washed with brine, and then dried. Removal of the solvent gave a residue, which was purified with column chromatography [0.5 g silica gel, 1:2 to 3:1 (gradient) EtOAc–hexane as eluents] to afford acetoxy-4-butanolide **48** (6.3 mg, 68% for 4 steps) as a colorless syrup: $R_f = 0.53$ (9:1 EtOAc–hexane); $[\alpha]_D^{23.2}$ +48.6 (*c* 0.27, $CHCl_3$); IR (neat) 1040, 1180, 1230, 1375, 1435, 1460, 1540, 1695, 1710, 1745, 1765, 1790, 2860, 2930, 3340 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, $J = 6.7$ Hz), 1.18–1.36 (m, 12H), 1.46–1.61 (m, 4H), 1.96–2.05 (m, 2H), 2.02 (s, 6H), 2.09 (s, 3H), 2.12 (s, 3H), 2.38 (t, 4H, $J = 7.4$ Hz), 4.49 (d, 1H, $J = 11.4$ Hz), 4.56 (d, 1H, $J = 11.4$ Hz), 4.76 (dd, 1H, $J = 4.9$ and 7.8 Hz), 5.33 (bdd, 1H, $J = 7.8$ and 15.3 Hz), 5.53 (dd, 1H, $J = 7.8$ and 7.8 Hz), 5.80 (d, 1H, $J = 4.9$ Hz), 5.86 (dt, 1H, $J = 15.3$ and 7.2 Hz), 5.97 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.5, 20.6, 21.1, 22.5, 22.7, 23.7, 23.8, 28.2, 28.9, 29.0, 31.6, 32.3, 42.7, 42.8, 62.4, 62.9, 70.4, 71.6, 77.2, 80.6, 122.0, 139.5, 168.1, 169.2, 169.6, 170.2, 171.7, 211.6; EI-MS *m/z* 567 (M^+, 1.2%), 507 (11.0), 449 (4.7), 448 (18.7), 423 (4.3), 422 (16.2), 390 (1.2), 389 (6.9), 388 (26.7), 382 (1.1), 381 (7.1), 380 (35.7), 348 (4.0), 347 (22.2), 346 (88.5), 277 (100); EI-HRMS Calcd for $C_{29}H_{45}NO_{10}$ (M^+): 567.3044, Found: *m/z* 567.3046.

(*E*,2*S*,3*R*,4*R*,5*S*)-2-Amino-3,4,5-trihydroxy-2-hydroxymethyl-14-oxo-icos-6-enoic Acid [Sphingofungin E (2)]. To a solution of acetoxy-4-butanolide **48** (3.0 mg, 0.053 mmol) in MeOH (0.6 mL) was added 10% aqueous NaOH solution (0.6 mL) at 25 °C. The mixture was stirred at 70 °C for 2 h, and then neutralized with IRC-76 resin (H^+ type) at 25 °C. Insoluble materials were filtered off, and the filtrate was concentrated to give a residue, which was purified by column chromatography [0.5 g silica gel, 1:1:8 to 1:1:3 (gradient) H_2O–MeOH–$CHCl_3$ (lower phase) as eluents] to afford sphingofungin E (**2**) (2.0 mg, 88%) as white crystals: $R_f = 0.23$ (1:3 MeOH–$CHCl_3$); Mp 144.0–145.8 °C; $[\alpha]_D^{25.0}$ −5.6 (*c* 0.14, MeOH); IR (KBr) 1060, 1105, 1195, 1270, 1385, 1405, 1465, 1500, 1505, 1640, 1715, 2855, 2930, 3200, 3360 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.94 (t, 3H, $J = 6.7$ Hz), 1.21–1.45 (m, 12H), 1.48–1.60 (m, 4H), 1.98–2.10 (m, 2H), 2.43 (t, 4H, $J = 7.4$ Hz), 3.63 (d, 1H, $J = 7.3$ Hz), 3.84 (d, 1H, $J = 11.0$ Hz), 3.94 (bs, 1H), 3.97 (d, 1H, $J = 11.0$ Hz), 4.10 (dd, 1H, $J = 7.6$ and 7.6 Hz), 5.44 (dd, 1H, $J = 7.6$ and 15.4 Hz), 5.77 (dt, 1H, $J = 15.4$ and 6.3 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 14.4, 23.6, 24.8, 24.9, 30.02, 30.03, 30.15, 30.18, 32.8, 33.4, 43.47, 43.51, 64.9, 70.0, 71.2, 75.6, 76.3, 130.2, 135.7, 173.2, 214.4; FAB-MS *m/z* 418 (M + H, 25.9%), 55 (100); FAB-HRMS Calcd for $C_{21}H_{40}NO_7$ (M + H)$^+$: 418.2805, Found: *m/z* 418.2805. The spectral data were fully identical with those of the authentic sample.[4j]

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