Total Synthesis of Grahamimycin A_1

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(3*R*)- and (3*S*)-3-Hydroxybutanoates were respectively converted into (2*E*,5*R*)- and (2*E*,5*S*)-5-*t*-butyldimethylsiloxy-2-hexenoic acids, corresponding to the O-1–C-6 fragment of grahamimycin A_1 (**1**). The O-7–C-14 fragment [(4*S*,5*S*,7*R*)- or (4*R*,5*R*,7*R*)-7-hydroxy-4,5-isopropylidenedioxyoctanoate] was synthesized from 4,6-dideoxy-α-D-*xylo*-hexopyranoside. Condensation of the both fragments, followed by deprotection at the terminal hydroxyl- and carboxyl-functions afforded the seco acids of the precursors of **1**. While the reaction of the seco acids having 13*S*-configuration with diethyl azodicarboxylate and triphenylphosphine afforded the corresponding lactones in low yields, macrolactonization of the seco acid having 13*R*-configuration by Yamaguchi procedure gave the desired lactone in 56% yield. Deprotection of *vic*-diol moiety of the lactone indicated the completion of relay synthesis of **1**.

Macrocyclic dilactones can be divided into unsymmetrical macrodiolides such as grahamimycins A_1 (**1**),[1] A (**2**),[2] B (**3**),[2] and colletodiol (**4**)[3] and C_2-symmetrical macrodiolides representatives pyrenophorin (**5**),[4] vermiculine (**6**),[5] conglobatin (**7**),[6] and elaiophylin (**8**)[7] (Scheme 1). The synthetic study of the latter class of compounds has been extensively carried out since 1970s and a variety of approaches have been reported.[4—7] On the other hand, unsymmetrical macrodiolides went largely unnoticed until 1980 when grahamimycin A_1 (**1**) isolated from the fungus *Cytospora* was reported to exhibit significant antibacterial activity against a variety of pathogenic microorganisms.[1a]

The structural elucidation of the former class of compounds has been mainly established in past decade. Thus, the absolute configuration of colletodiol (**4**) originally proposed by MacMillan and Simpson,[3d] has been revised by Seebach and co-workers based on X-ray crystallographic analysis in 1981.[3c] The structure of grahamimycin A (**2**) and B (**3**) has been determined by Gurusiddaiah and Ronald in 1981.[2] In 1982, Seebach established the absolute configuration of grahamimycin A_1 (**1**) through the total synthesis of (*S,S*)-(+)-grahamimycin A_1, unnatural inactive enantiomer of **1**.[1b] (*S,S*)-(+)-Grahamimycin A_1 has also been prepared by Ghiringhelli in 1983.[1f]

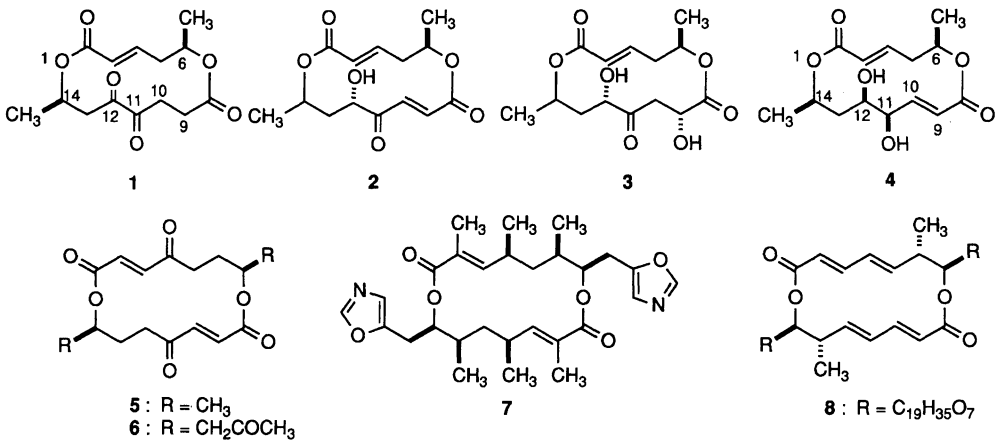
Confirmation of the absolute structures of colletodiol and grahamimycin A_1 reveals that the two macrolides could be correlated by redox reactions. Thus, oxidation of the *vic*-diol system (C-11 and C-12) and reduction of C-9–C-10 double bond of colletodiol formally yields grahamimycin A_1.

The total synthesis of (*R,R*)-(−)-grahamimycin A_1 (**1**) has been reported by Hillis and Ronald in 1985[1c] and Bestmann and Schobert in 1987,[1d] while colletodiol (**4**) was synthesized by Seebach et al. (1984),[3g] Keck et al. (1989),[3i] and by us (1984).[3f] We wish to report herein relay synthesis of grahamimycin A_1 (**1**).

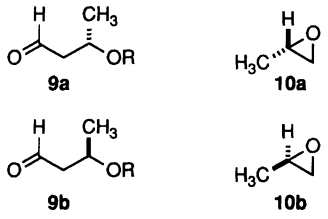
One of the most crucial problems in the synthesis of macrolide antibiotics and analogues is selection of enantiomerically pure starting materials having a suitable constitution and a functional group pattern which are readily incorporated into the chiral target structure.[8] Seidel and Seebach have utilized 3-(*S*)-hydroxybutanal (**9a**) and (*S*)-methyloxirane (**10a**) as starting materials for the preparation of the O-1–C-6 fragment and the O-7–C-14 fragments of (*S,S*)-grahamimycin A_1.[1b] 3-(*S*)-Hydroxybutanal was used by Ghiringhelli in his synthesis of (*S,S*)-grahamimycin-A_1.[1f] (*R*)-Methyloxirane (**10b**) has been correlated to the C-2 and C-8 asymmetric carbon atoms of (*R,R*)-grahamimycin A_1 by Hillis and Ronald,[1c] while Bestmann and Schobert have selected 3-(*R*)-hydroxybutanal (**9b**) as common chiral source of both asymmetric centers of grahamimycin A_1[1d] (Scheme 2). 3-(*S*)- and 3-(*R*)-Hydroxybutanal can be readily prepared by the reduction of the corresponding 3-hydroxybutanoates.[9]

Grahamimycin A_1 has only two asymmetric carbon atoms, the structure being unique in containing *vic*-diketo group which could be formally derived from the corresponding *vic*-diol system. Although it was difficult to estimate in a priori fashion which macrocyclization sequence would be more successful for the construction of grahamimycin A_1 skeleton, we selected the preparation and union of two appropriately protected hydroxy acids.[10] Scheme 3 represents the retrosynthetic analysis and strategic bond disconnections defining the key compounds **13** and **14** for an eventual total synthesis of **1**. In view of successful synthesis of colletodiol,[3f] the bond forming of both fragments would be accomplished by esterification (O-1–C-2; grahamimycin A_1 numbering) and macrolactonization (O-7–C-8 or C-6–O-7; grahamimycin A_1 numbering).

Apart from the strategies for constructing carbon-chain framework with appropriate sense of chirality, the choice of protecting groups is also an important problem for the success of the synthesis. In order to avoid the difficulty of protecting group manipulation experienced in the synthesis of colletodiol,[3f] *t*-butyldi-



Scheme 1.



Scheme 2.

methylsilyl (TBDMS) group and 2-(*p*-tolylsulfonyl)ethyl (PTSE) group were chosen as protecting groups for hydroxyl function of **13** and carboxyl function of **14** so as to remove simultaneously after connection of both segments.[11]

(2*E*,5*R*)-5-Hydroxy-2-hexenoic acid (**13a**) and its enantiomer (**13b**) would be respectively prepared from readily available (*R*)- and (*S*)-3-hydroxybutanoic acids (**15a** and **15b**) which have been utilized as chiral building blocks in synthesis of a variety of natural products.[8a,9]

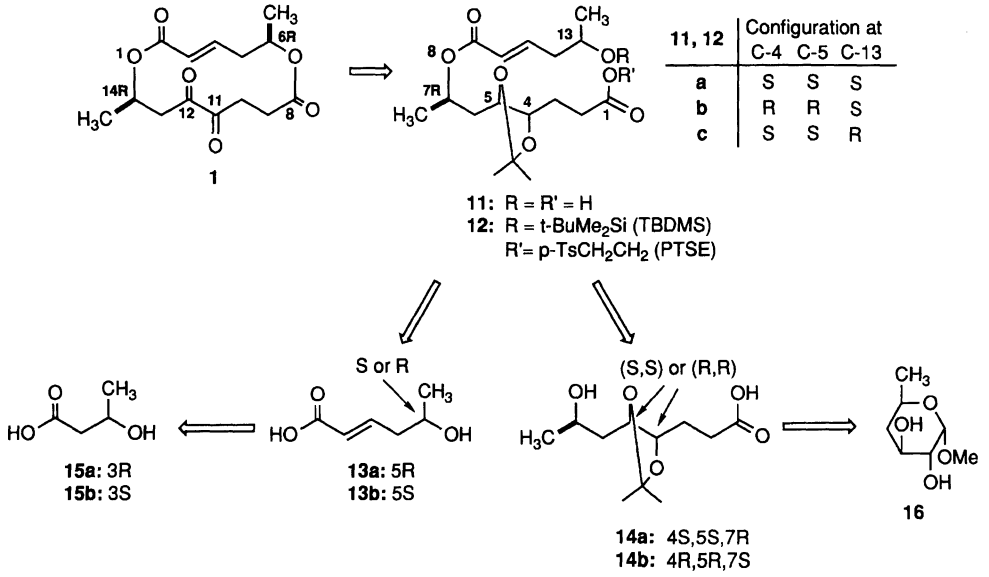
4,5,7-Trihydroxyoctanoic acids (**14**) would be generated from polyoxygenated substrates such as carbohydrates. The sense of chirality at the C-7 of **14** coincides with C-5 of D-aldohexose; hence hydroxyl groups at C-2 and C-3 of the hexose can be correlated with C-4 and C-5 of **14**. Thus, deoxygenation at the positions 4 and 6 of the hexose and two carbon elongation at C-1 affords **14**. In order to asses the any effect of the configuration at the C-2 and C-3 on the macrolactonization, 2-(*p*-tolylsulfonyl)ethyl (4*S*,5*S*,7*R*)- and (4*R*,5*R*,7*R*)-7-hydroxy-4,5-isopropylidenedioxyoctanoates (**14a**, **14b**) were prepared from *xylo*-hexopyranose and *arabino*-hexopyranose derivatives, respectively. The advantage of the use of D-hexose as starting material is taken of the fact that the structure of the D-hexose is independent to the target molecule because the hydroxyl groups at C-2 and C-3 are oxidized to *vic*-diketo functionality in the course of the synthesis. We postponed the diketone formation to the last step of the synthesis.

Results and Discussion

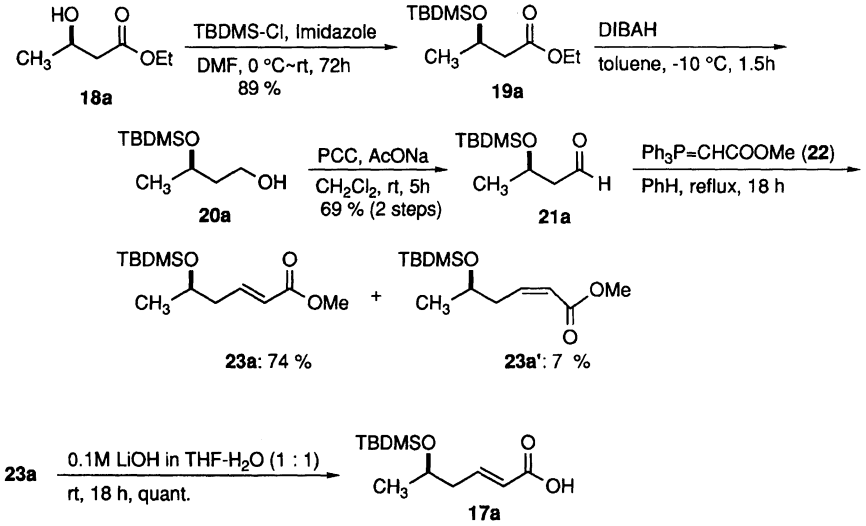
Preparation of O-1–C-6 Fragment. The O-1–C-6 fragment, (2*E*,5*R*)- or (2*E*,5*S*)-5-*t*-butyldimethylsiloxy-2-hexenoic acid (**17a**, **17b**), was synthesized from (3*R*)- or (3*S*)-3-hydroxybutanoic acid ester (**18a**, **18b**). Thus, ethyl (*R*)-3-hydroxybutanoate (**18a**) prepared from poly(3-hydroxybutanoic acid) by known procedure[9a,9b] reacted with *t*-butyldimethylsilyl (TBDMS) chloride to give the corresponding TBDMS ether **19a** in 89% yield.[12a] Reduction of **19a** with diisobutylaluminium hydride (DIBAH)[12b] and subsequent oxidation of the resulting alcohol **20a** by pyridinium chlorochromate (PCC) in the presence of AcONa afforded the corresponding aldehyde **21a** in 69% yield.[13,14a] Aldehyde **21a** reacted with methoxycarbonylmethylenetriphenylphosphorane (**22**) giving methyl (2*E*,5*R*)-5-*t*-butyldimethylsiloxy-2-hexenoate (**23a**) in 74% yield along with the corresponding *Z*-isomer (**23a′**). Hydrolysis of **23a** with LiOH (0.1 M, 1 M=1 mol dm^{-3}) in THF–H_2O (1 : 1) at room temperature proceeded smoothly to give (2*E*,5*R*)-5-*t*-buthyldimethylsiloxy-2-hexenoic acid (**17a**) in nearly quantitative yield (Scheme 4).

By a similar manner, *t*-butyl (*S*)-3-hydroxybutanoate (**18b**) gave TBDMS ether **19b** which was converted into (3*S*)-3-(*t*-butyldimethylsiloxy)butanal (**21b**) in 67% yield via alcohol **20b**. Alternatively, when **19b** reacted with DIBAH in toluene at −70°C for 3 h, aldehyde **21b** was isolated in 76% yield.[14b] The reaction of **21b** with **22** gave **23b** and **23b′** in 54 and 10% yields, respectively. Saponification of **23a** under the conditions described above gave (2*E*,5*S*)-5-*t*-butyldimethylsiloxy-2-hexenoic acid (**17b**) in quantitative yield (Scheme 5).

Synthesis of O-7–C-14 Fragment. The O-7–C-14 fragments, 2-(*p*-tolylsulfonyl)ethyl esters of (4*S*,5*S*,7*R*)- and (4*R*,5*R*,7*R*)-7-hydroxy-4,5-isopropylidenedioxyoctanoates (**24a**, **24b**) were synthesized from 4,6-dideoxy-α-D-*xylo*-hexopyranoside (**25**).[15] Hydrolysis of **25** afforded the correspond-



Scheme 3.

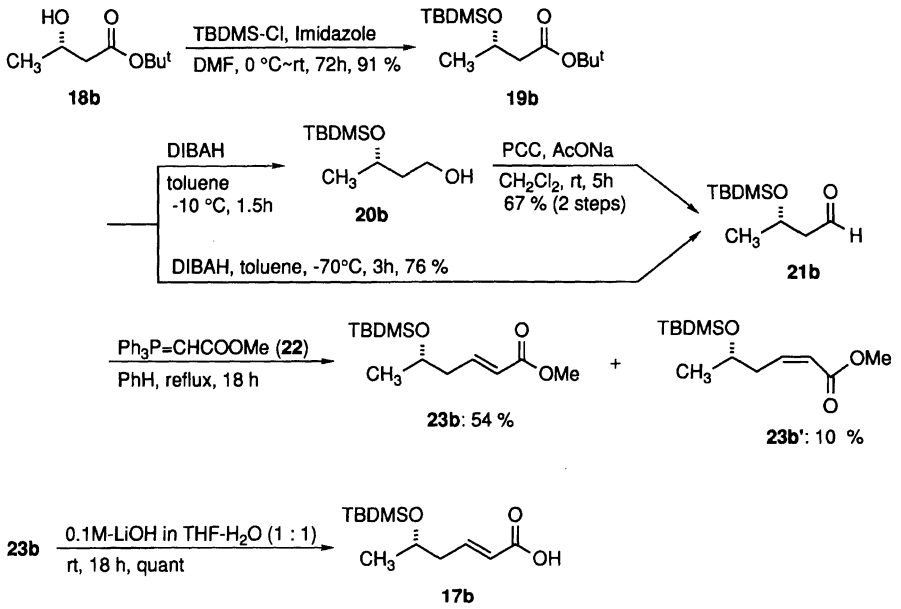


Scheme 4.

ing free sugar **26a** in 84% yield. The reaction of **26a** with 2-(*p*-tolylsulfonyl)ethoxycarbonylmethylenetriphenylphosphorane (**27**),[16] followed by acetonidation afforded 2-(*p*-tolylsulfonyl)ethyl (2*E*,4*S*,5*S*,7*R*)-7-hydroxy-4,5-isopropylidenedioxy-2-octenoate (**28a**) in 41% yield from **26a**. Hydrogenation of **28a** afforded the desired O-7–C-14 fragment **24a** in quantitative yield (Scheme 6).

In order to prepare appropriately protected (4*R*,5*R*,7*R*)-4,5,7-trihydroxyoctanoate **24b**, the configurations at the C-2 and C-3 of **25** were inverted via 2,3-anhydropyranoside.[17a] Tosylation of **25** afforded 2-*O*-tosyl derivative **29** and 3-*O*-tosyl derivative **29'** in 68% yield in a ratio of 5.8 : 1. The mixture reacted with MeONa in methanol to yield methyl 2,3-anhydro-α-D-*lyxo*-hexopyranoside (**30**) in 50% isolated yield. The compound **30** was treated with 1 M KOH under reflux for 2 h, the desired 4,6-dideoxy-α-D-*arabino*-hexopyranoside (**31**) being obtained in 91% yield without any detectable formation of **25**. Following the procedure described in the preparation of **24a**, **31** was converted into 2-(*p*-tolylsulfonyl)ethyl (2*E*,4*R*,5*R*,7*R*)-7-hydroxy-4,5-isopropylidenedioxy-2-octenoate (**24b**) in 12% overall yield from **31** (Scheme 6).

Synthesis of Seco Acids. In the course of our synthetic study of colletodiol and related compounds, intermolecular dehydration between α,β-unsaturated carboxylic acid and long chain secondary alcohol with reactive esterification reagents was studied.[17b] Thus, when 2-butenoic acid or 2-pentenoic acid was allowed to react with 2-octanol and 1-ethyl-2-bromopyridinium tetrafluoroborate in the presence of tributylamine,[19a] the corresponding 1-methylheptyl 3-alkenoate **32** or **33** was obtained in 51 or 70% yield, respectively, rather than



Scheme 5.

expected α, β-unsaturated esters. The migration of the double bond could be explained by assuming the intermediacy of ketene **34** (Scheme 7).[18,19] Although the reaction would be utilized for the preparation of β,γ-unsaturated carboxylic ester from a thermodynamically more stable α,β-conjugated acid, the procedure could not be applicable to the present purpose.

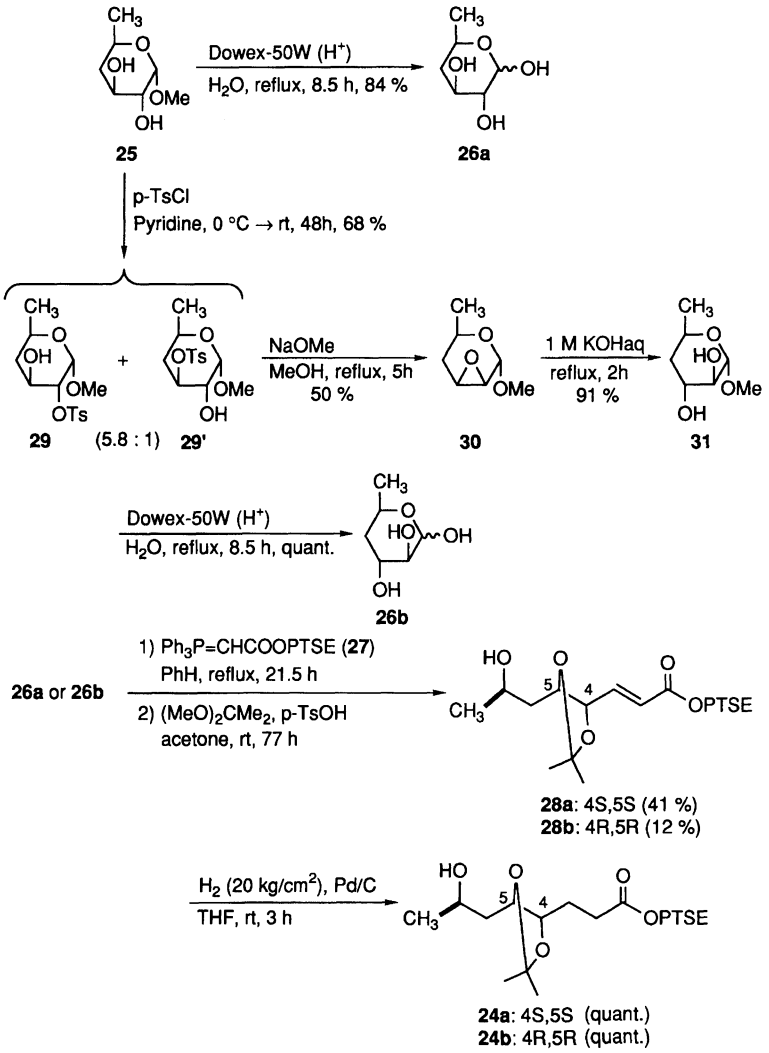
When (2*E*,5*S*)-5-tetrahydropyranyloxyhexenoic acid (**35**) reacted with *t*-butyl (4*R*,5*R*,7*R*)-7-hydroxy-4,5-isopropylidenedioxyoctanoate (**36**) under Stegrich conditions [dicyclohexylcarbodiimide (DCC; 1.5 molar amount) with catalytic amount of 4-dimethylaminopyridine (DMAP)],[20] the expected ester **37** was obtained in 27% yield along with considerable amount of *N*-acylurea (**38**) (Scheme 7).[18,21]

In the condensation of unreactive α,β-unsaturated carboxylic acid with bulky secondary alcohol, therefore, the reaction system must be chosen such that the intermediary acylating reagent formed do not collapse to less reactive species under the reaction conditions used.

The reaction system of choice was Yamaguchi method,[22] because this procedure was successfully utilized in a variety of macrolactonization under rather drastic conditions (toluene reflux for several hours). Thus, **17a** was treated with 2,4,6-trichlorobenzoyl chloride in the presence of triethylamine in THF at room temperature for 2 h, filtered, and the filtrate was evaporated. The resulting mixed anhydride was allowed to react with **24a** in the presence of DMAP in toluene at room temperature for 24 h to afford protected seco acid (**39a**) in 50% yield. Under the same conditions, fully protected seco acids **39b** and **39c** were prepared in 95 and 85% yields, respectively (Scheme 8).

Although the protecting groups of the carboxyl and hydroxyl functionalities of **39a**, **39b**, or **39c** would be removed by a single operation, the reactivities toward fluoride ion are different. Thus, the silyl ether of secondary alcohol is hardly cleaved under the conditions where PTSE group is completely removed [3 molar amount of tetrabutylammonium fluoride (TBAF) in THF, 0°C, 1 h].[23] Metcalf et al. have demonstrated that $LiBF_4$ is effective for the cleavage of *t*-butyldimethylsilyl (TBDMS) secondary alkyl ether.[24] Thus, fully protected seco acid **39c** was treated with $LiBF_4$ (1.5 molar amount) in THF at room temperature for 25 h where the silyl group was completely removed but PTSE group still remained. Therefore the resulting mixture was treated with TBAF (3 molar amount) for 18 h at room temperature to give seco acid **40c** and 2-(*p*-tolylsulfonyl)ethyl ester **41** in 50 and 50% yields, respectively (Table in Scheme 9; Entry 1). When **39c** was treated with TBAF (1.5 molar amount) for 1.5 h to remove PTSE group and any silyl group, followed by $LiBF_4$(3 molar amount), it took 64 h to complete removal of the remaining silyl group (Table in Scheme 9; Entry 2). It was found that both PTSE group and TBDMS group simultaneously removed when **39c** was treated with TBAF (3 molar amount) in THF at room temperature for 64 h to afford the desired seco acid **40c** in nearly quantitative yield (Table in Scheme 9; Entry 3). Seco acids **40a** and **40b** were also synthesized by the treatment of **39a** and **39b** with TBAF in THF at room temperature for 72 h (Table in Scheme 9; Entries 4 and 5). In these experiments, no ester bond cleavage could be detected.[25]

Lactonization. Since the configuration of the reaction site of seco acids **40a** and **40b** is *S*, the configuration of the chiral center must be inverted. This event would be carried out by the reaction of the seco acid with diethyl azodicarboxylate (DEAD) and triphenyl-



Scheme 6.

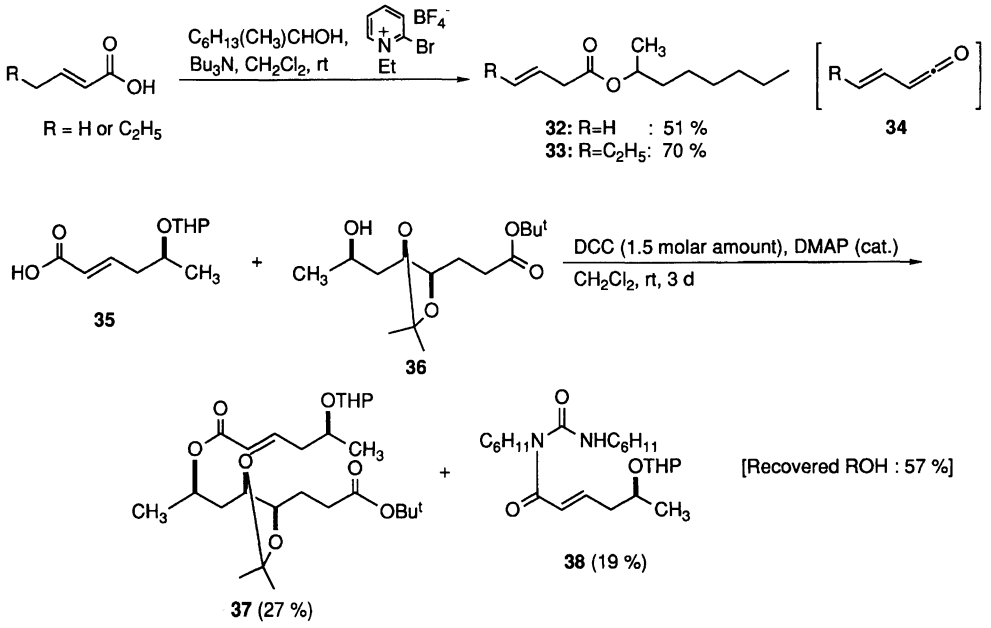
phosphine (TPP) where lactonization with inversion at the chiral center of the seco acid could be expected.[26] Thus, the lactonization of the appropriately protected seco acid of colletodiol with 4*R*,5*R*,7*R*,13*S* configuration (**42**) by the use of DEAD and TPP afforded the fully protected colletodiol **43** in 45% yield after recrystallization (Scheme 10).[3f]

In view of the fact, **40a** was allowed to react with DEAD and TPP in toluene at −10°C for 24 h and then at room temperature for 42 h in which lactone **44a** was obtained but the yield was unexpectedly low (12% isolated yield; Scheme 11). The difference between **40a** and **42** is the partial structure of C-2–C-5 segments. Thus, in the hope to obtain any information about the effect of configurations at C-4 and C-5 on lactonization, the reaction of **40b** with DEAD and TPP was attempted but the yield of the desired lactone **44b** was again low (4% isolated yield) (Scheme 11).

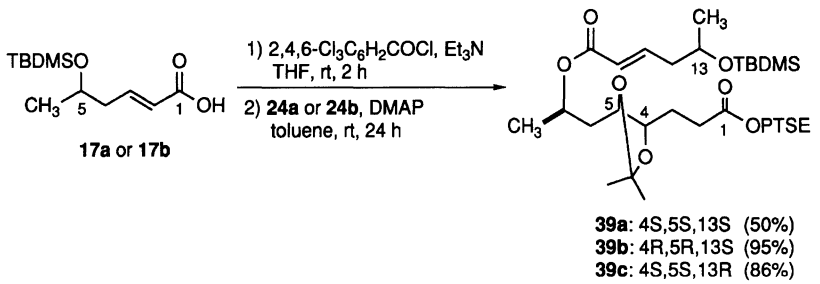
Although no side products could be isolated and identified in the lactonization of **40a** and **40b**, β-elimination would be the most likely side reaction.[26] This assumption would be supported by the reaction of 2-(*p*-tolylsulfonyl)ethyl (*S*)-5-hydroxyhexenoate (**45**) with (4*S*,5*S*,7*R*)-octanoic acid (**46**), DEAD, and TPP where 2-(*p*-tolylsulfonyl)ethyl 2,4-hexadienoic acid was obtained in 46% yield rather than expected ester **47** (Scheme 12).[27,28]

The successful lactonization of **42** suggests that the hydroxyl group and carboxyl group of **42** are brought so close together as to facilitates intramolecular lactonization. In contrast, structural change at the C-2 and C-3 separates the reaction sites of seco acids **40a** and **40b** causing lactonization difficult at least at low temperature. At the present stage of investigation, however, the principal factor decisive in the ease of lactonization is not clear.[29]

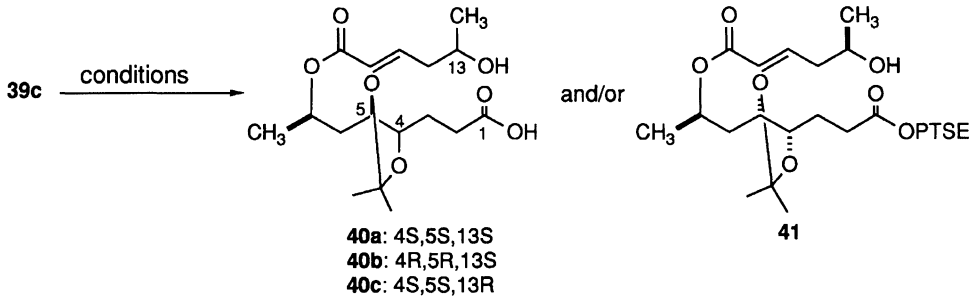
Based on the consideration described above, in order to cyclize a conformationally rigid substrate, the lactonization procedure must be selected such that the reaction could be carried out at elevated temperature. Thus, lactonization by Yamaguchi procedure was next examined. Yamaguchi esterification proceeds with retention of configuration at the hydroxyl functions, seco acid **40c** was treated with 2,4,6-trichlorobenzoyl chlo-



Scheme 7.

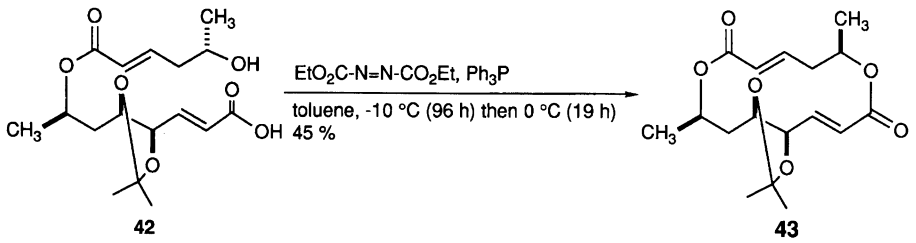


Scheme 8.

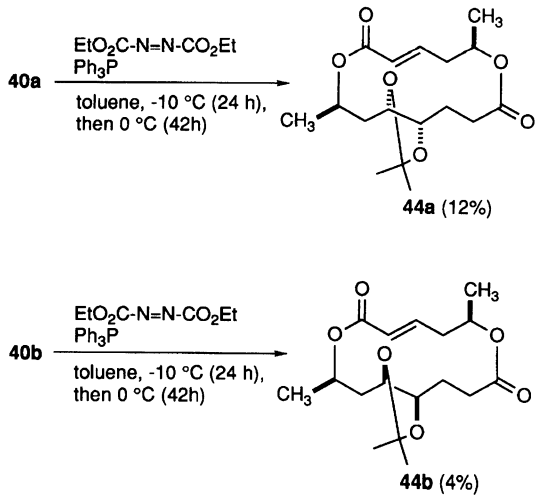


Entry	substrate	conditions	product(s) / yield
1	**39c**	1) $LiBF_4$ (1.5 molar amount), THF, rt, 25 h 2) TBAF (3 molar amount), THF, rt, 18 h	**40c**/50% and **41**/50 %
2		1) TBAF (1.5 molar amount), THF, rt, 1.5 h 2) $LiBF_4$ (3 molar amount), THF, rt, 64 h	**40c**/quant.
3		TBAF (3 molar amount), THF, rt, 64 h	**40c**/quant.
4	**39a**	TBAF (3 molar amount), THF, rt, 72 h	**40a**/quant.
5	**39b**	TBAF (3 molar amount), THF, rt, 72 h	**40b**/quant.

Scheme 9.



Scheme 10.



Scheme 11.

ride and triethylamine in THF at room temperature for 2 h. Triethylamine hydrochloride was filtered off and the filtrate was diluted with toluene. The resulting solution was added dropwise to toluene containing DMAP (7 molar amount) over a period of 5.5 h at 95°C and the mixture was stirred for 30 min at this temperature to give lactone **44a** in 56% yield (Scheme 13). Methanolysis of the acetonide group of **44a** gave diol **48** in 78% yield. Since conversion of **48** into grahamimycin A_1 has already been reported by Bestmann and Schobert,[1d] the preparation of **48** indicate completion of relay synthesis of grahamimycin A_1 (Scheme 13).

Experimental

General. Melting points were measured on a micro melting point apparatus (Yanagimoto Seisakusyo) and were uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on JEOL-GX270 spectrometer in $CDCl_3$. Chemical shifts were reported in ppm relative to tetramethylsilane (0 ppm) as the internal standard. For the compounds having t-butyldimethylsilyl group, $CHCl_3$ (7.26 ppm) in $CDCl_3$ was used as the internal standard. Data were reported as follows: chemical shift (multiplicity, integrated intensity, coupling constants). Following abbreviation are used for spin multiplicity; s=singlet, d=doublet, t=triplet, q=quartet, qu=quintet, sx=sextet, br=broad, m=multiplet. Mass spectra were recorded on a JEOL-JMS-SX102 mass spectrometer. Optical rotations were measured on a JASCO-DIP-370 photoelectric polarimeter. Silica gel column chromatography were performed on Merck Kieselgel 60 (Art 7734) or Wakogel C-300. In general, organic solvents were purified and dried by the appropriate procedure. Air and moisture sensitive reactions were carried out under N_2 or Ar atmosphere. *t*-Butyl 3-(*S*)-hydroxybutanoate was obtained from Chisso Co., Ltd. Poly-(*R*)-3-hydroxybutanoic acid was obtained commercially from Fluka.

Methoxycarbonylmethylenetriphenylphosphorane (22). This compound was prepared according to the previously outlined procedure[30] in 41% yield (11.2 g): Mp 170—173°C. Lit,[30b] mp 169—169.5°C.

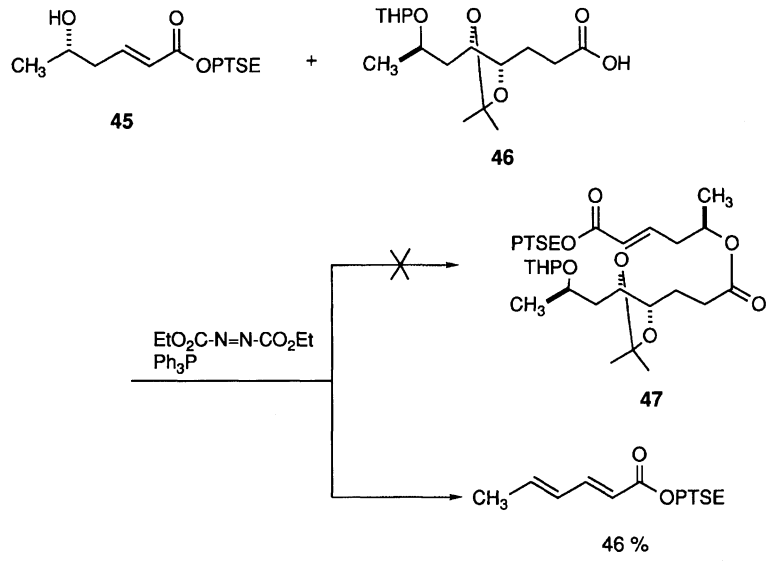
2- (*p*- Tolylsulfonyl)ethoxycarbonylmethylenetriphenylphosphorane (27). This compound was prepared according to the reported procedures.[16,31]

Ethyl (*R*)-3-Hydroxybutanoate (18a). This compound was prepared by reported procedure.[9a,9b] Bp 66°C/8 mmHg (1 mmHg =133.322 Pa), $[\alpha]_D^{22}$ −44.1° (*c* 1.10, $CHCl_3$); Lit,[9a] bp 86—86.5°C/22 mmHg, $[\alpha]_D^{21}$ −43.4° (*c* 1.36, $CHCl_3$).

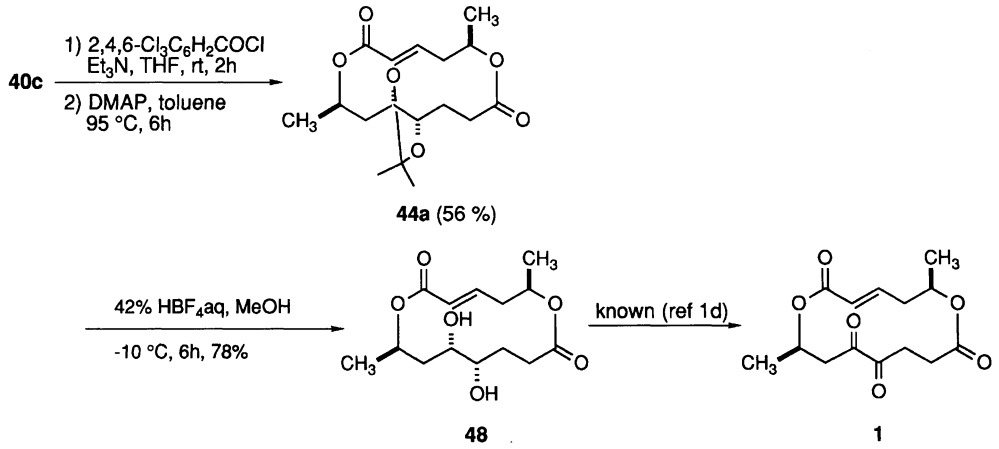
Ethyl (*R*)-3-*t*-Butyldimethylsiloxybutanoate (19a). A solution of **18a** (3.81 g, 28.9 mmol), *t*-butyldimethylsilyl chloride (5.25 g, 34.7 mmol), and imidazole (4.97 g, 73.0 mmol) in dimethylformamide (70 ml) was stirred at room temperature for 72 h. To the reaction mixture was added water and ether and phases were separated. The ether layer was washed with saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl solution, dried with $MgSO_4$, and concentrated. The residue was distilled under reduced pressure (75°C/3—4 mmHg) to afford **19a** in 89% yield (6.32 g): $[\alpha]_D^{18}$ −26.9° (*c* 1.02, $CHCl_3$); ^{1}H NMR δ=4.27 (dqd, 1H, C3–H, *J*=7.4, 6.3, 5.6 Hz), 4.12 (qd, 2H, Et–CH_2, *J*=7.1, 1.9 Hz), 2.47 (dd, 1H, C2–H, *J*=14.4 Hz), 2.35 (dd, 1H, C2–H′), 1.26 (t, 3H, Et–CH_3), 1.19 (d, 3H, C4–H), 0.86 (s, 9H, *t*-Bu), 0.06 (s, 3H, Si–CH_3), 0.04 (s, 3H, Si–CH_3').

(*R*)-3-*t*-Butyldimethylsiloxy-1-butanol (20a). To a stirred solution of **19a** (4.68 g, 19 mmol) in toluene was added 1 M diisobutylaluminium hydride in dichloromethane (47.5 ml, 47.5 mmol) at −10°C over 1.5 h and the mixture was stirred at −10°C for 1.5 h. The reaction mixture was quenched with aqueous saturated sodium tartrate solution and filtered. The filtrate was extracted with dichloromethane and dichloromethane layer was dried with $MgSO_4$ and concentrated. The residue was distilled under reduced pressure (82°C/1.2 mmHg) to afford **20a** in 76% yield (2.74 g): $[\alpha]_D^{18}$ −30.1° (*c* 1.09, $CHCl_3$). ^{1}H NMR δ=4.06 (qud, 1H, C3–H, *J*=4.4, 6.3 Hz), 3.78 (dddd, 1H, C1–H, *J*=10.8, 4.6, 6.6 Hz), 3.67 (dddd, 1H, C1–H′, *J*=7.7, 4.7 Hz), 2.80 (t, 1H, C1–OH, *J*=5.0 Hz), 1.73 (ddt, 1H, C2–H, *J*=14.2, 4.4 Hz), 1.59 (dddd, 1H, C2–H′, *J*=6.3 Hz), 1.16 (d, 3H, C4–H), 0.85 (s, 9H, *t*-Bu), 0.05 (s, 3H, Si–CH_3), 0.04 (s, 3H, Si–CH_3'). Lit,[14a] bp (racemic form) 39—42°C/0.02 mmHg.

(*R*)-3-*t*-Butyldimethylsiloxybutanal (21a). To a suspension of pyridinium chlorochromate (PCC: 6.44 g, 27.8



Scheme 12.



Scheme 13.

mmol) and sodium acetate (570 mg, 6.95 mmol) in dichloromethane (30 ml) was added **20a** (2.84 g, 13.9 mmol) in dichloromethane (30 ml) and the mixture was stirred at room temperature for 5 h. To the reaction mixture was added ether and filtered through a Florisil® and the filtrate was concentrated to afford **21a** as syrup in 91% yield (2.57 g). The aldehyde was used without further purification: $[\alpha]_D^{16}$ $-14.4°$ (c 1.05, $CHCl_3$); ^1H NMR $\delta=9.78$ (t, 1H, C1–H, $J=2.4$ Hz), 4.34 (dtd, 1H, C3–H, $J=7.0$, 6.3, 5.1 Hz), 2.54 (ddd, 1H, C2–H, $J=15.7$ Hz), 2.44 (ddd, 1H, C2–H′), 1.23 (d, 3H, C4–H), 0.86 (s, 9H, t-Bu), 0.06 (s, 3H, Si–CH_3), 0.05 (s, 3H, Si–CH_3'). Lit,[14a] bp (racemic form) 80°C/0.02 mmHg.

Methyl (2*E*,5*R*)-5-*t*-Butyldimethylsiloxy-2-hexenoate (23a). This compound was prepared by the modified procedure reported for the preparation of the corresponding racemic form.[14a] A solution of **21a** (1.19 g, 5.9 mmol) and **22** (2.17 g, 6.5 mmol) in benzene (80 ml) was refluxed for 19 h. The reaction mixture was concentrated and chromatographed on silica gel with ether and petroleum ether (1 : 40, v/v) to afford **23a** as syrup in 74% yield (1.13 g) and methyl (2*Z*, 5*R*)-5-*t*-butyldimethylsiloxy-2-hexenoate (**23a′**) in 7% yield (100 mg): ^1H NMR *E*-isomer: $\delta=6.94$ (dt, 1H, C3–H, $J=15.7$, 1.4 Hz), 5.82 (dt, 1H, C2–H, $J=1.4$ Hz), 3.91 (sx, 1H, C5–H, $J=6.0$ Hz), 3.71 (s, 3H, $COOCH_3$), 2.30 (ddt, 2H, C4–H, $J=1.4$ Hz), 1.14 (d, 3H, C6–H), 0.86 (s, 9H, t-Bu), 0.03 (s, 3H, Si–CH_3), 0.02 (s, 3H, Si–CH_3'). Lit,[14a] bp (racemic form) 75°C/0.02 mmHg. *Z*-isomer: $\delta=6.36$ (dt, 1H, C3–H, $J=11.5$, 7.3 Hz), 5.84 (dt, 1H, C2–H, $J=1.7$ Hz), 3.95 (dqd, 1H, C5–H, $J=5.3$, 6.2, 6.3 Hz), 3.69 (s, 3H, $COOCH_3$), 2.82 (dddd, 1H, C4–H, $J=15.2$ Hz), 2.75 (dddd, 1H, C4–H′), 1.15 (d, 3H, C6–H), 0.87 (s, 9H, t-Bu), 0.04 (s, 3H, Si–CH_3), 0.03 (s, 3H, Si–CH_3').

(2*E*,5*R*)-5-*t*-Butyldimethylsiloxy-2-hexenoic Acid (17a). This compound was prepared by the modified procedure reported for the preparation of the corresponding racemic form.[14a] To a suspension of **23a** (258 mg, 1 mmol) in tetrahydrofuran (THF) and water (1 : 1, 30 ml) was added lithium hydroxide monohydrate (126 mg, 3 mmol) and the mixture was stirred at room temperature for 18 h. The reaction mixture was washed with chloroform and the aqueous layer was acidified to pH 3.5 with Dowex-50W(H^+). The solution was extracted with chloroform, dried with $MgSO_4$ and concentrated to afford **17a** as syrup in quantitative

yield (277 mg). This was used without further purification: ^{1}H NMR δ=9—11 (br, 1H, COOH), 7.08 (dt, 1H, C3–H, J=15.5, 7.3 Hz), 5.84 (dt, 1H, C2–H, J=1.3 Hz), 3.95 (sx, 1H, C5–H, J=6.2, 6.0 Hz), 2.35 (ddt, 2H, C4–H, J=1.3 Hz), 1.17 (d, 3H, C6–H), 0.88 (s, 9H, *t*-Bu), 0.05 (s, 3H, Si–CH_3), 0.04 (s, 3H, Si–CH_3'). Lit,[14a] bp (racemic form) 120°C/0.01 mmHg.

***t*-Butyl (*S*)-3-*t*-Butyldimethylsiloxybutanoate (19b).** A solution of **18b** (8.01 g, 50 mmol), *t*-butyldimethylsilyl chloride (9.04 g, 60 mmol) and imidazole (8.5 g, 125 mmol) in dimethylformamide (80 ml) was stirred at room temperature for 72 h. To the reaction mixture was added water and ether and phases were separated. The ether layer was successively washed with saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl solution, dried with $MgSO_4$, and concentrated. The residue was distilled under reduced pressure (79°C/1 mmHg) to afford **19b** in 91% yield (12.5 g): $[\alpha]_D^{20}$+21.6° (*c* 1.03, $CHCl_3$); ^{1}H NMR δ=4.25 (dqd, 1H, C3–H, J=6.8, 5.9, 6.3 Hz), 2.43 (dd, 1H, C2–H, J=14.8 Hz), 2.28 (dd, 1H, C2–H′), 1.46 (s, 9H, COO*t*-Bu), 1.17 (d, 3H, C4–H), 0.89 (s, 9H, Si–*t*-Bu), 0.08 (s, 3H, Si–CH_3), 0.07 (s, 3H, Si–CH_3').

(*S*)-3-*t*-Butyldimethylsiloxy-1-butanol (20b). To a stirred solution of **19b** (11.0 g, 40 mmol) in toluene was added 1 M diisobutylaluminium hydride in dichloromethane (100 ml, 100 mmol) at −10°C over 1.5 h and the mixture was stirred at −10°C for 1.5 h. The reaction mixture was quenched with aqueous saturated sodium tartrate and filtered. The filtrate was extracted with dichloromethane. Dichloromethane layer was dried with $MgSO_4$ and concentrated. The residue was distilled under reduced pressure (80°C/2 mmHg) to afford **20b** in 81% yield (6.59 g): $[\alpha]_D^{24}$+29.8° (*c* 1.00, $CHCl_3$); ^{1}H NMR δ=4.10 (qud, 1H, C3–H, J=6.5, 4.2 Hz), 3.83 (ddd, 1H, C1–H, J=10.9, 7.9, 4.1 Hz), 3.71 (ddd, 1H, C1–H′, J=6.2, 6.3 Hz), 2.38 (br, 1H, C1–OH), 1.78 (ddt, 1H, C2–H, J=14.2, 4.2 Hz), 1.63 (dddd, 1H, C2–H′, J=6.6 Hz), 1.19 (d, 3H, C4–H), 0.89 (s, 9H, *t*-Bu), 0.08 (s, 3H, Si–CH_3), 0.07 (s, 3H, Si–CH_3').

(*S*)-3-*t*-Butyldimethylsiloxybutanal (21b). To a suspension of PCC (14.3 g, 62 mmol) and sodium acetate (1.27 g, 15.5 mmol) in dichloromethane (60 ml) was added **20b** (6.33 g, 31.0 mmol) in dichloromethane (60 ml) and the mixture was stirred at room temperature for 6 h. To the reaction mixture was added ether and filtered through Florisil® and the filtrate was concentrated to afford **21b** as syrup in 83% yield (5.23 g). The aldehyde was used without further purification: ^{1}H NMR δ=9.8 (t, 1H, C1–H, J=2.6 Hz), 4.36 (qud, 1H, C3–H, J=7.0, 5.9, 5.0 Hz), 2.56 (ddd, 1H, C2–H, J=15.7 Hz), 2.46 (ddd, 1H, C2–H′), 1.24 (d, 3H, C4–H), 0.87 (s, 9H, *t*-Bu), 0.08 (s, 3H, Si–CH_3), 0.06 (s, 3H, Si–CH_3').

Methyl (2*E*,5*S*)-5-*t*-Butyldimethylsiloxy-2-hexenoate (23b). A solution of **21b** (5.23 g, 25.6 mmol) and **22** (10 g, 30 mmol) in benzene (200 ml) was refluxed for 18 h. The reaction mixture was concentrated and chromatographed on silica gel with ether and petroleum ether (1:20, v/v) to afford **23b** as syrup in 54% yield (3.57 g) and methyl (2*Z*,5*S*)-5-*t*-butyldimethylsiloxy-2-hexenoate (**23b′**): For *E*-isomer, $[\alpha]_D^{18}$+8.94° (*c* 1.01, $CHCl_3$); ^{1}H NMR *E*-isomer: δ=6.95 (dt, 1H, C3–H, J=15.5, 7.5 Hz), 5.83 (dt, 1H, C2–H, J=1.5 Hz), 3.92 (sx, 1H, C5–H, J=6.0, 5.9 Hz), 3.72 (s, 3H, $COOCH_3$), 2.31 (ddt, 2H, C4–H, J=1.5 Hz), 1.15 (d, 3H, C6–H), 0.87 (s, 9H, *t*-Bu), 0.04 (s, 3H, Si–CH_3), 0.03 (s, 3H, Si–CH_3'). For *Z*-isomer: δ=6.36 (dt, 1H, C3–H, J=11.5, 7.3 Hz), 5.84 (dt, 1H, C2–H, J=1.7 Hz), 3.95 (dqd, 1H, C5–H, J=5.3, 6.2, 6.3 Hz), 3.69 (s, 3H, $COOCH_3$), 2.82 (dddd, 1H, C4–H, J=15.2 Hz), 2.75 (dddd, 1H, C4–H′), 1.15 (d, 3H, C6–H), 0.87 (s, 9H, *t*-Bu), 0.04 (s, 3H, Si–CH_3), 0.03 (s, 3H, Si–CH_3').

(2*E*,5*S*)-5-*t*-Butyldimethylsiloxy-2-hexenoic Acid (17b). To a suspension of **23b** (258 mg, 1 mmol) in THF and water (1:1, 30 ml) was added lithium hydroxide monohydrate (126 mg, 3 mmol) and the mixture was stirred at room temperature for 18 h. The reaction mixture was washed with chloroform and the aqueous layer was acidified to pH 3.5 with Dowex-50W(H^+). The solution was extracted with chloroform, dried with $MgSO_4$, and concentrated to afford **17b** as syrup in quantitative yield (250 mg). This was used without further purification: ^{1}H NMR δ=9—12 (br, 1H, COOH), 7.08 (dt, 1H, C3–H, J=15.5, 7.7 Hz), 5.84 (dt, 1H, C2–H, J=1.2 Hz), 3.95 (sx, 1H, C5–H, J=6.0, 6.1 Hz), 2.35 (ddt, 2H, C4–H, J=1.1 Hz), 1.17 (d, 3H, C6–H), 0.88 (s, 9H, *t*-Bu), 0.05 (s, 3H, Si–CH_3), 0.04 (s, 3H, Si–CH_3').

Methyl 4,6-Dichloro-4,6-dideoxy-α-D-galactopyranoside. This compound was prepared by a literature procedure[15a] in 36% yield (22.2 g): Mp 157—159°C; $[\alpha]_D^{17}$+179° (*c* 0.99, H_2O); ^{1}H NMR δ=4.85 (d, 1H, C1–H, J=5.8 Hz), 4.53 (dd, 1H, C4–H, J=3.5, 0.8 Hz), 4.15 (td, 1H, C5–H, J=6.6 Hz), 4.00 (ddd, 1H, C3–H, J=3.6, 6.8 Hz), 3.85 (td,1H, C2–H, J=9.2 Hz), 3.68 (d, 2H, C6–H), 3.48 (s, 3H, C1–OCH_3), 2.61 (d, 1H, C3–OH), 2.20 (d, 1H, C2–OH). Lit,[15a] mp 158°C; $[\alpha]_D^{20}$+179° (*c*=2.1, H_2O).

Methyl 4,6-Dideoxy-α-D-*xylo*-hexopyranoside (25). This compound was prepared according to reported procedure[15b] in 79% yield (4.32 g): Mp 100—101°C; $[\alpha]_D$ +171° (*c* 0.4, MeOH); ^{1}H NMR δ=4.74 (d, 1H, C1–H, J=3.8 Hz), 3.90 (ddd, 1H, C5–H, J=2.0, 11.9, 6.3 Hz), 3.83 (tdd, 1H, C3–H, J=9.2, 3.0, 4.9, 9.2 Hz), 3.40 (s, 3H, C1–OCH_3), 3.39 (td, 1H, C2–H, J=9.4 Hz), 3.25 (d, 1H, C3–OH), 2.78 (d, 1H, C2–OH), 1.98 (ddd, 1H, C4–H′, J=12.7 Hz), 1.36 (q, 1H, C4–H), 1.21 (d, 3H, C6–H). Lit,[15b] mp 105—108°C: $[\alpha]_D^{20}$+171° (*c* 1.0, MeOH).

Methyl 4,6-Dideoxy-2-*O*-tosyl-α-D-*xylo*-hexopyranoside (29). To a solution of **25** (4.87 g, 30 mmol) in pyridine (100 ml) was added tosyl chloride (6.86 g, 36 mmol) in pyridine (30 ml) at 0°C and the solution was stirred for 48 h at room temperature. To the solution was added water and extracted with chloroform. The organic layer was successively washed with 10% H_2SO_4 and saturated aqueous $NaHCO_3$. The organic layer was dried with $MgSO_4$ and concentrated. The residue was chromatographed on silica gel with benzene–ethyl acetate (7:1, v/v) to afford the mixture (6.41 g) of **29** and 3-*O*-tosyl derivative **29′** as syrup. The yields of **29** and **29′** were estimated to be 58 and 10% by ^{1}H NMR spectroscopy. This was used without further purification. ^{1}H NMR for **29** δ=7.84 (d, 2H, Aryl–H, J=8.1 Hz), 7.35 (d, 2H, Aryl–H′), 4.63 (d, 1H, C1–H, J=3.6 Hz), 4.23 (dd, 1H, C2–H, J=9.5 Hz), 4.09 (ddd, 1H, C3–H, J=11.3, 5.2 Hz), 3.90 (ddd, 1H, C5–H, J=11.5, 2.2, 6.2 Hz), 3.25 (s, 3H, C1–OCH_3), 2.44 (s, 3H, tolyl–CH_3), 2.04 (ddd, 1H, C4–H′, J=13.0 Hz), 1.86 (br, 1H, C3–OH), 1.38 (ddd, 1H, C4–H), 1.17 (d, 3H, C6–H).

Methyl 2,3-Anhydro-4,6-dideoxy-α-D-*lyxo*-hexopy-

ranoside (30). To a solution of **29** and **29'** (6.42 g, 20.3 mmol) in methanol (60 ml) was added 1 M sodium methoxide in methanol (24.3 ml) and the mixture was refluxed for 5 h. To the cooled solution was added water and the mixture was extracted with chloroform. The organic layer was dried with $MgSO_4$ and concentrated. The residue was chromatographed on silica gel with petroleum ether–ether (5:1, v/v) and distilled under reduced pressure (60°C/12 mmHg) to afford **30** in 50% yield (1.46 g): $[\alpha]_D$ +69.2° (*c* 0.6, MeOH); ^{1}H NMR δ=4.88 (s, 1H, C1–H), 3.84 (dqd, 1H, C5–H, J=11.1, 4.4, 6.3 Hz), 3.44 (s, 3H, C1–OCH_3), 3.33 (dd, 1H, C3–H, J=3.9, 15.3 Hz), 2.97 (d, 1H C2–H), 1.91 (ddd, 1H, C4–H'), 1.74 (dd, 1H, C4–H), 1.13 (d, 3H, C6–H). Lit,[32] bp 45—80°C/16 mmHg; mp 28—30°C; $[\alpha]_D^{20}$ +70° (*c* 1.0, MeOH).

Methyl 4,6-Didexoy-α-D-*arabino*-hexopyranoside (31). A suspension of **30** (1.69 g, 11.7 mmol) in 1 M aqueous KOH (35 ml) was refluxed for 2 h. The cooled mixture was neutralized with glacial acetic acid and concentrated. To the residue was added chloroform and the mixture was filtered through Hyflo Super-Cel®. The filtrate was dried with $MgSO_4$, concentrated, and distilled under reduced pressure (95°C/0.8 mmHg) to afford **31** in 91% yield (1.36 g): $[\alpha]_D$ +101° (*c* 0.6, MeOH); ^{1}H NMR δ=4.68 (s, 1H, C1–H), 4.11 (dqd, 1H, C5–H, J=10.2, 3.3, 6.3 Hz), 3.87 (m, 1H, C3–H, J=3.5, 9.9, 3.3, 3.5 Hz), 3.61 (dd, 1H, C2–H, J=7.6 Hz), 3.49 (d, 1H, C3–OH), 3.44 (s, 3H, C1–OCH_3), 2.42 (d, 1H, C2–OH), 1.82 (ddd, 1H, C4–H, J=14.2 Hz), 1.70 (dt, 1H, C4–H'), 1.24 (d, 3H, C6–H).

4,6-Dideoxy-D-*xylo*-hexopyranose (26a). A suspension of **25** (4 g, 24.7 mmol) and Dowex-50W(H^+) (12 g) in water (64 ml) was refluxed for 8.5 h, cooled and concentrated. The residue was recrystallized from ethanol–petroleum ether to afford **31** in 84% yield (3.07 g): Mp 137—140°C; $[\alpha]_D$ +39.9° (*c* 0.5, H_2O). Lit,[15b] mp 136—137°C; $[\alpha]_D^{20}$ +100° → +34° (*c* 1.0, H_2O).

4,6-Dideoxy-D-*arabino*-hexopyranose (26b). A suspension of **31** (2.38 g, 14.7 mmol) and Dowex-50W(H^+) (7 g) in water (32 ml) was refluxed for 8.5 h, cooled and concentrated to afford **26b** as syrup in quantitative yield (2.26 g). This was used without further purification.

2-(*p*-Tolylsulfonyl)ethyl (2*E*,4*S*,5*S*,7*R*)-7-Hydroxy-4,5-isopropylidenedioxy-2-octenoate (28a). A solution of **26a** (1.08 g, 7.2 mmol) and **27** (6.1 g, 10.8 mmol) in benzene (50 ml) was refluxed for 21.5 h. The reaction mixture was cooled and concentrated. The residue was chromatographed on silica gel with chloroform-methanol (20:1, v/v) to afford crude 2-(*p*-tolylsulfonyl)ethyl (2*E*,4*S*,5*S*,7*R*)-4,5,7-trihydroxy-2-octenoate. The crude product was dissolved in acetone (20 ml) and to the solution was added 2, 2-dimethoxypropane (3.58 g, 34.4 mmol) and p-toluenesulfonic acid (0.18 g, 1 mmol). The mixture was stirred for 77 h at room temperature. The reaction mixture was cooled to 0°C and to the mixture was added 0.3 M solution of sodium methoxide in methanol until a neutral solution was obtained. The mixture was filtered through Hyflo Super-Cel® and the filtrate was concentrated. The residue was chromatographed on silica gel with ether and recrystallized form hexane–ethyl acetate to afford **28a** in 41% yield (1.22 g): Mp 78—79°C; $[\alpha]_D$ −17.5° (*c* 0.5, $CHCl_3$); ^{1}H NMR δ=7.80 (d, 2H, Ph–H, J=8.1 Hz), 7.37 (d, 2H, Ph–H'), 6.79 (dd, 1H, C3–H, J=15.7, 5.4 Hz), 5.92 (dd, 1H, C2–H, J=1.3 Hz), 4.47 (t, 2H, $COOCH_2$, J=6.1 Hz), 4.18 (ddd, 1H, C4–H, J=8.5 Hz), 4.00—4.11 (m, 1H, C7–H, J=4.0, 6.3 Hz), 3.93 (ddd, 1H, C5–H), 3.47 (t, 2H, SO_2–CH_2), 2.46 (s, 3H, Ph–CH_3), 2.14 (d, 1H, C7–OH), 1.69—1.74 (m, 2H, C6–H), 1.45 (s, 3H, isop-CH_3), 1.41 (s, 3H, isop-CH_3'), 1.24 (d, 3H, C8–H). Found: C, 58.31; H, 6.84%. Calcd for $C_{20}H_{28}O_7S$: C, 58.30; H, 6.84%.

2-(*p*-Tolylsulfonyl)ethyl (2*E*,4*R*,5*R*,7*R*)-7-Hydroxy-4,5-isopropylidenedioxy-2-octenoate (28b). A solution of **26b** (0.17 g, 1.1 mmol) and **27** (0.61 g, 1.2 mmol) in benzene (25 ml) was refluxed for 18 h. The reaction mixture was cooled and concentrated. The residue was chromatographed on silica gel with chloroform–methanol (7:1, v/v) to afford crude 2-(*p*-tolylsulfonyl)ethyl (2*E*,4*S*,5*S*,7*R*)-4,5,7-trihydroxy-2-octenoate. The crude product was dissolved in acetone (3.7 ml) and to the solution was added 2, 2-dimethoxypropane (0.69 g, 6.7 mmol) and *p*-toluenesulfonic acid (0.023 g, 0.13 mmol). The mixture was stirred for 64 h at room temperature. The reaction mixture was cooled to 0°C and to the mixture was added 1 M solution of sodium methoxide in methanol until a neutral solution was obtained. The mixture was filtered through Hyflo Super-Cel® and the filtrate was concentrated. The residue was chromatographed on silica gel with ether and recrystallized from hexane–ethyl acetate to afford **28b** in 12% yield (0.13 g): Mp 86°C; $[\alpha]_D$ +7.7° (*c* 0.5, $CHCl_3$); ^{1}H NMR δ=7.80 (d, 2H, Ph–H, J=8.1 Hz), 7.37 (d, 2H, Ph–H'), 6.77 (dd, 1H, C3–H, J=15.7, 1.5 Hz), 5.93 (dd, 1H, C2–H, J=1.5 Hz), 4.48 (t, 2H, $COOCH_2$, J=6.1 Hz), 4.15 (ddd, 1H, C4–H, J=8.4 Hz), 3.93—4.07 (m, 1H, C7–H, J=5.9 Hz), 3.93 (td, 1H, C5–H), 3.47 (t, 2H, SO_2–CH_2), 2.81 (br, 1H, C7–OH), 2.46 (s, 3H, Ph–CH_3), 1.64—1.76 (m, 2H, C6–H), 1.45 (s, 3H, isop-CH_3), 1.42 (s, 3H, isop-CH_3'), 1.22 (d, 3H, C8–H). Found: C, 58.18; H, 6.96%. Calcd for $C_{20}H_{28}O_7S$: C, 58.30; H, 6.84%.

2-(*p*-Tolylsulfonyl)ethyl (4*S*,5*S*,7*R*)-7-Hydroxy-4,5-isopropylidenedioxyoctanoate (24a). The compound **28a** (0.41 g, 1 mmol) in THF (50 ml) was hydrogenated in the presence of 10%-Pd/C (0.1 g) under 20 kg cm^{-2} of H_2 at room temperature for 3 h in an autoclave. The reaction mixture was concentrated to afford **24a** as syrup in quantitative yield (0.42 g). This was used without further purification: ^{1}H NMR δ=7.80 (d, 2H, Ph–H, J=8.1 Hz), 7.38 (d, 2H, Ph–H'), 4.40 (t, 2H, COO–CH_2, J=6.2 Hz), 4.05 (dqd, 1H, C7–H, J=4.2, 7.2, 6.3 Hz), 3.84 (td, 1H, C5–H, J=8.3, 7.2, 4.4 Hz), 3.63 (td, 1H, C4–H, J=3.2, 8.3 Hz), 3.44 (t, 2H, SO_2–CH_2), 2.46 (s, 3H, Ph–CH_3), 2.2—2.4 (br, 1H, C7–OH), 2.34 (ddd, 1H, C2–H, J=16.9, 8.7, 8.8 Hz), 2.24 (ddd, 1H, C2–H', J=6.9, 8.4 Hz), 1.85 (dddd, 1H, C3–H, J=13.9 Hz), 1.57—1.74 (m, 3H, C3–H' and C6–H), 1.37 (s, 3H, isop-CH_3), 1.36 (s, 3H, isop-CH_3'), 1.23 (d, 3H, C8–H).

2-(*p*-Tolylsulfonyl)ethyl (4*R*,5*R*,7*R*)-7-Hydroxy-4,5-isopropylidenedioxyoctanoate (24b). The compound **28b** (0.38 g, 0.93 mmol) in THF (50 ml) was hydrogenated in the presence of 10%-Pd/C (0.2 g) under 20 kg cm^{-2} of H_2 at room temperature for 3 h in an autoclave. The reaction mixture was concentrated to afford **24b** as syrup in quantitative yield (0.42 g). This was used without further purification: ^{1}H NMR δ=7.79 (d, 2H, Ph–H, J=8.2 Hz), 7.37 (d, 2H, Ph–H'), 4.41 (td, 2H, COO–CH_2, J=6.2, 1.2 Hz), 4.00 (dqd, 1H, C7–H, J=3.0, 9.2, 6.3 Hz),

3.71 (td, 1H, C5–H, J=9.2, 8.2, 3.4 Hz), 3.59 (td, 1H, C4–H, J=3.2, 8.2 Hz), 3.42 (t, 2H, SO_2–CH_2), 3.06 (br, 1H, C7–OH), 2.45 (s, 3H, Ph–CH_3), 2.34 (ddd, 1H, C2–H, J=16.8, 8.8, 6.1 Hz), 2.25 (ddd, 1H, C2–H′, J=6.9, 8.2 Hz), 1.84 (dddd, 1H, C3–H, J=14.0 Hz), 1.51—1.73 (m, 3H, C3–H′ and C6–H), 1.37 (s, 3H, isop-CH_3), 1.36 (s, 3H, isop-CH_3'), 1.20 (d, 3H, C8–H).

2-(*p*-Tolylsulfonyl)ethyl (10*E*,4*S*,5*S*,7*R*,13*R*)-, (10*E*,4*S*,5*S*,7*R*,13*S*)-, and (10*E*,4*R*,5*R*,7*R*,13*S*)-13-*t*-Butyldimethylsiloxy-4,5-isopropylidenedioxy-7-methyl-9-oxo-8-oxa-10-tetradecenoates (39c, 39a, and 39b). To a solution of 2,4,6-trichlorobenzoyl chloride (0.366 g, 1.5 mmol) in THF (1.5 ml) was added **17a** (0.250 g, 1 mmol) and triethylamine (0.250 g, 1.5 mmol) in THF (1.5 ml) over 30 min and the mixture was stirred for additional 2 h at room temperature. The mixture was filtered under Ar and the filtrate was evaporated. The resulting anhydride was dissolved in toluene (1 ml). To the mixture was added **24a** (0.415 g, 1 mmol) and DMAP (0.135 g, 1.1 mmol) in toluene (5 ml) and stirred for 22 h at room temperature. The reaction mixture was filtered through Hyflo Super-Cel® and concentrated. The residue was chromatographed on silica gel with benzene–ethyl acetate (20:1, v/v) to afford **39c** as syrup in 86% yield.

The compound **39a** and **39b** were synthesized as syrup in a similar manner as above (50 and 95%, respectively).

39a: ^{1}H NMR δ=7.79 (d, 2H, Ph–H, J=8.3 Hz), 7.36 (d, 2H, Ph–H′), 6.93 (dt, 1H, C11–H, J=7.7, 15.6 Hz), 5.81 (dt, 1H, C10–H, J=1.2 Hz), 5.09 (dqd, 1H, C7–H, J=4.4, 6.2, 8.5 Hz), 4.39 (t, 2H, $COOCH_2$, J=6.0 Hz), 3.91 (sx, 1H, C13–H, J=6.0 Hz), 3.61 (td, 1H, C2–H, J=2.5, 8.4 Hz), 3.51 (td, 1H, C2–H′, J=2.9, 8.2 Hz), 3.43 (t, 2H, SO_2–CH_2), 2.45 (s, 3H, Ph–CH_3), 2.15—2.36 (m, 4H, C4–H, C5–H, C12–H), 1.82 (ddd, 1H, C6–H, J=2.5, 8.5, 14.2 Hz), 1.65 (ddd, 1H, C6–H′, J=4.4, 8.9 Hz), 1.73—1.86 (m, 1H, C3–H), 1.55—1.70 (m, 1H, C3–H′), 1.33 (s, 3H, isop-CH_3), 1.30 (s, 3H, isop-CH_3'), 1.28 (d, 3H, C7–CH_3), 1.15 (d, 3H, C13–CH_3), 0.87 (s, 9H, *t*-Bu), 0.04 (s, 3H, Si–CH_3), 0.03 (s, 3H, Si–CH_3').

39b: ^{1}H NMR δ=7.79 (d, 2H, Ph–H, J=7.9 Hz), 7.36 (d, 2H, Ph–H′), 6.93 (dt, 1H, C11–H, J=7.7, 15.6 Hz), 5.80 (dt, 1H, C10–H, J=1.2 Hz), 5.13 (sx, 1H, C7–H, J=6.3 Hz), 4.38 (td, 2H, $COOCH_2$, J=6.2 Hz), 3.91 (sx, 1H, C13–H, J=6.3 Hz), 3.64 (td, 1H, C2–H, J=3.9, 7.9 Hz), 3.56 (td, 1H, C2–H′, J=2.9, 8.2 Hz), 3.43 (t, 2H, SO_2–CH_2), 2.45 (s, 3H, Ph–CH_3), 2.14—2.39 (m, 4H, C4–H, C5–H, C12–H), 1.92 (ddd, 1H, C6–H, J=0.7, 6.5, 14.1 Hz), 1.60 (ddd, 1H, C6–H′, J=6.2, 8.3 Hz), 1.66—1.86 (m, 2H, C3–H), 1.33 (s, 3H, isop-CH_3), 1.31 (s, 3H, isop-CH_3'), 1.28 (d, 3H, C7–CH_3), 1.15 (d, 3H, C13–CH_3), 0.87 (s, 9H, *t*-Bu), 0.04 (s, 3H, Si–CH_3), 0.03 (s, 3H, Si–CH_3').

39c: ^{1}H NMR δ=7.77 (d, 2H, Ph–H, J=8.2 Hz), 7.35 (d, 2H, Ph–H′), 6.90 (dt, 1H, C11–H, J=6.9, 15.5 Hz), 5.79 (dt, 1H, C10–H, J=1.4 Hz), 5.02 (dqd, 1H, C7–H, J=4.5, 6.3, 8.4 Hz), 4.37 (t, 2H, $COOCH_2$, J=6.2 Hz), 3.91 (sx, 1H, C13–H, J=6.0 Hz), 3.59 (td, 1H, C2–H, J=2.5, 8.5 Hz), 3.50 (td, 1H, C2–H′, J=3.0, 8.3 Hz), 3.41 (t, 2H, SO_2–CH_2), 2.43 (s, 3H, Ph–CH_3), 2.13—2.34 (m, 2H, C4–H, C5–H), 2.29 (ddd, 2H, C12–H, J=1.4 Hz) 1.80 (ddd, 1H, C6–H, J=2.4, 8.4, 14.2 Hz), 1.63 (ddd, 1H, C6–H′, J=4.5, 9.0 Hz), 1.73—1.83 (m, 1H, C3–H), 1.53—1.64 (m, 1H, C3–H′), 1.31 (s, 3H, isop-CH_3), 1.28 (s, 3H, isop-CH_3'), 1.27 (d, 3H, C7–CH_3), 1.14 (d, 3H, C13–CH_3), 0.85 (s, 9H, *t*-Bu), 0.02 (s, 3H, Si–CH_3), 0.01 (s, 3H, Si–CH_3').

(10*E*,4*S*,5*S*,7*R*,13*S*)-, (10*E*,4*R*,5*R*,7*R*,13*S*)-, and (10*E*,4*S*,5*S*,7*R*,13*R*)-13-Hydroxy-4,5-isopropylidenedioxy-7-methyl-9-oxo-8-oxa-10-tetradecenoic acids (40a, 40b, and 40c). To a solution of **39c** (1.4 g, 2.1 mmol) in THF (30 ml) was added 1 M TBAF in THF (6.3 ml, 6.3 mmol) and the mixture was stirred for 72 h at room temperature. The reaction mixture was extracted with 0.1 M aqueous $NaHCO_3$ and water layer was acidified to pH 4 with Dowex-50W(H^+). The solution was extracted with chloroform and organic layer was dried with $MgSO_4$ and concentrated to afford **40c** as syrup in quantitative yield (665 mg). This was used without further purification.

The compound **40a** and **40b** were prepared as syrup in a similar manner as above in quantitative yield.

Macrolactonization Using DEAD-TPP System: (3*E*,6*R*,11*S*,12*S*,14*R*)- or (3*E*,6*R*,11*R*,12*R*,14*R*)-11,12-Isopropylidenedioxy-6,14-dimethyl-1,7-dioxa-3-cyclotetradecene-2,8-tetrone (44a, 44b). To a solution of **40a** (44 mg, 0.13 mmol) in toluene (5 ml) was added triphenylphosphine (68 mg, 0.26 mmol) in toluene (5 ml) and diethyl azodicarboxylate (45 mg, 0.26 mmol) at −10°C. The mixture was stirred at −10°C for 24 h then 0°C for 42 h. The reaction mixture was evaporated and chromatographed on silica gel with ether–petroleum ether (1:1, v/v) to afford **44a** (crystals, mp 57—59°C) in 12% yield (5 mg).

The isomer **44b** (syrup) was prepared in a similar manner as above in 4% yield.

44a: $[\alpha]_D$ −6.3° (*c* 0.7, $CHCl_3$); ^{1}H NMR δ=6.76 (ddd, 1H, C4–H, J=6.1, 9.9, 15.7 Hz), 5.86 (dt, 1H, C3–H, J=0.9 Hz), 4.94 (dqd, 1H, C6–H, J=2.9, 6.3, 12.9 Hz), 4.92 (dqd, 1H, C14–H, J=2.4, 6.0, 10.0 Hz), 3.79 (ddd, 1H, C11–H, J=2.6, 7.1, 9.9 Hz), 3.67 (ddd, 1H, C12–H, J=2.5, 9.3 Hz), 2.57 (ddd, 1H, C9–H, J=7.7, 11.3, 13.3 Hz), 2.47 (dddd, 1H, C5–H, J=12.9 Hz), 2.29 (dddd, 1H, C5–H′), 2.23 (ddd, 1H, C9–H′, J=3.2, 10.1 Hz), 2.08 (dt, 1H, C13–H, J=14.9 Hz), 1.97 (ddd, 1H, C13–H′), 1.74 (dtd, 1H, C10–H, J=13.8 Hz), 1.62 (dddd, 1H, C10–H′), 1.38 (s, 3H, isop-CH_3), 1.35 (s, 3H, isop-CH_3'), 1.34 (d, 3H, C6–CH_3), 1.31 (d, 3H, C14–CH_3); FAB MS (75 eV) m/z 327 $(M+H)^+$; HRMS Calcd for $(C_{17}H_{26}O_6+H)^+$: M, 327.1808. Found: 327.1829.

44b: ^{1}H NMR δ=6.78 (ddd, 1H, C4–H, J=7.5, 8.4, 15.8 Hz), 5.80 (dt, 1H, C3–H, J=1.0 Hz), 5.06—5.18 (m, 2H, C6–H, C14–H, J=3.2, 4.3, 4.5, 11.2 Hz), 3.84 (td, 1H, C11–H, J=2.9, 7.1 Hz), 3.73 (ddd, 1H, C12–H, J=3.1, 7.2, 9.2 Hz), 2.55 (ddd, 1H, C9–H, J=5.4, 11.6, 14.0 Hz), 2.28 (dddd, 1H, C5–H, J=11.2 Hz), 2.09 (ddd, 1H, C5–H′), 2.04 (ddd, 1H, C9–H′, J=3.1, 6.4 Hz), 1.82—1.94 (m, 2H, C13–H), 1.58—1.70 (m, 2H, C10–H), 1.38 (s, 3H, isop-CH_3), 1.36 (s, 3H, isop-CH_3'), 1.33 (d, 3H, C6–CH_3), 1.30 (d, 3H, C14–CH_3).

Macrolactonization Using Yamaguchi Method: (3*E*,6*R*,11*S*,12*S*,14*R*)-11,12-Isopropylidenedioxy-6,14-dimethyl-1,7-dioxa-3-cyclotetradecene-2,8-tetrone (44a). To a solution of **40c** (585 mg, 1.7 mmol) in THF (2 ml) was added triethylamine (344 mg, 3.4 mmol) in THF (4 ml) and 2,4,6-trichlorobenzoyl chloride (829 mg, 3.4 mmol) in THF (6 ml). The mixture was stirred for 2 h at room temperature and filtered under Ar. The filtrate was diluted with toluene (900 ml) and the mixture was added

dropwise to a solution of DMAP (1.454 g, 11.9 mmol) in toluene (200 ml) at 90°C over a period of 5 h. The mixture was stirred at 90°C for 1 h and cooled to room temperature. The mixture was diluted with ether (500 ml) and washed successively with saturated aqueous citric acid, saturated aqueous $NaHCO_3$ and water. The organic layer was dried with $MgSO_4$, evaporated, and chromatographed on silica gel with ether–petroleum ether (1 : 5, v/v) to afford **44a** in 56% yield (306 mg).

(3*E*,6*R*,11*S*,12*S*,14*R*)-11,12-Dihydroxy-6,14-dimethyl-1,7-dioxa-3-cyclotetradecene-2,8-tetrone (48). To a solution of **44a** (81 mg, 0.3 mmol) in methanol (5 ml) was added 42% aqueous HBF_4 (0.1 ml) and the mixture was stirred at 0°C for 6 h. The reaction mixture was added saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was dried with $MgSO_4$, evaporated, and chromatographed on silica gel with dichloromethane–methanol (20 : 1, v/v) to afford **48** as white needles (mp 90—92°C) in 78% yield (28 mg). $[\alpha]_D$ −48° (*c* 0.3, $CHCl_3$); ^{1}H NMR δ=6.78 (dt, 1H, C4–H, J=8.1, 15.8 Hz), 5.80 (dt, 1H, C3–H, J=1.2 Hz), 5.19 (dqd, 1H, C6–H, J=2.6, 6.3, 11.3 Hz), 5.06 (dqd, 1H, C14–H, J=3.2, 6.4, 10.7 Hz), 3.42 (ddd, 1H, C12–H, J=0.3, 5.0, 8.3 Hz), 3.22 (td, 1H, C11–H, J=7.2 Hz), 2.66—2.58 (br, 2H, C11–OH and C12–OH), 2.49 (ddd, 1H, C9–H, J=2.0, 11.3, 17.4 Hz), 2.41 (dddd, 1H, C5–H, J=13.5 Hz), 2.35 (dddd, 1H, C5–H′), 2.30 (ddd, 1H, C9–H′, J=2.2, 7.0 Hz), 1.96 (ddd, 1H, C13–H, J=14.4 Hz), 1.92 (ddd, 1H, C10–H, J=14.5 Hz), 1.79 (dtd, 1H, C10–H′), 1.71 (ddd, 1H, C13–H′), 1.33 (d, 3H, C14–CH_3), 1.29 (d, 3H, C6–CH_3); ^{13}C NMR ($CDCl_3$) δ=21.0 (q, 2C), 27.7 (t), 30.2 (t), 39.2 (t), 40.5 (t), 68.3 (d), 69.7 (d), 70.3 (d), 73.1 (d), 124.2 (d), 144.6 (d), 166.1 (s), 174.2 (s); FAB MS (75 eV) m/z 287 $(M+H)^+$; HRMS Calcd for $(C_{14}H_{22}O_6+H)^+$: M, 287.1495. Found: m/z 287.1533.

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