Tetrahedron Vol. 49, No. 27, pp. 5979-5996, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Stereoselective Total Synthesis of Polyether Ionophore Antibiotics, Isolasalocid A and Lasalocid A. Part 1. Stereocontrolled Construction of the C Rings (C_{18}-C_{24}) by Acid-Catalyzed Cyclization of *p*-Methoxyphenylallyl Alcohols.[1]

Kiyoshi Horita,* Ichio Noda, Kazuhiro Tanaka, Tamaki Miura, Yuji Oikawa, and Osamu Yonemitsu*

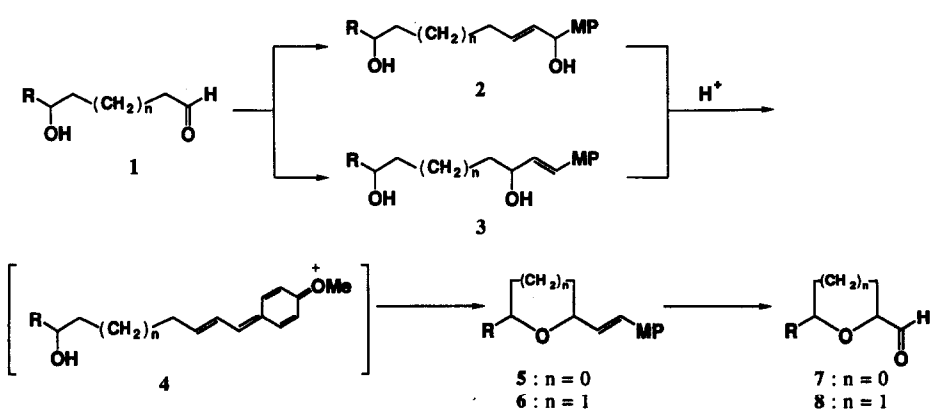
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

(*Received in Japan* 12 *March* 1993)

Keywords: polyether antibiotic; total synthesis; stereoselective synthesis; tetrahydrofuran; tetrahydropyran; acid-catalyzed cyclization

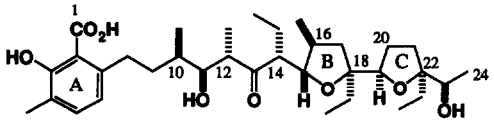
Abstract: The C_{18}-C_{24} subunits (**11**, **12**) of isolasalocid A (**9**) and lasalocid A (**10**) were synthesized stereoselectively *via* construction of the tetrahydrofuran and tetrahydropyran rings by acid-catalyzed cyclization of the corresponding *p*-methoxyphenylallyl alcohols (**18**, **25**).

In connection with the synthetic study of naturally occurring polyether ionophore antibiotics with very complex structures, many methods for the stereocontrolled construction of substituted tetrahydrofuran (THF) and tetrahydropyran (THP) rings, main structural units of the polyether antibiotics, have been reported, and some of them were successfully applied to the total synthesis of several antibiotics.[2,3] We also developed a new

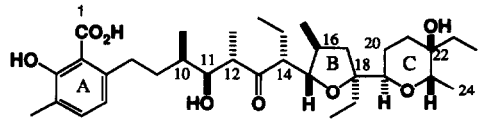


Scheme 1

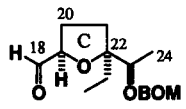
synthetic method of functionalized THF and THP (Scheme 1)[4] for the purpose of establishing a common synthetic methodology of the polyether antibiotics. When a *p*-methoxyphenyl (MP) substituted allyl alcohol (**2** or **3**) derived from an aldehyde (**1**) was treated with an acid, the acid-catalyzed cyclization *via* a cation intermediate (**4**) occurred to give THF (**5**) and THP (**6**), which were easily converted to the corresponding and more versatile aldehydes, **7** and **8**. In order to prove the superiority of this method, we applied it to a stereoselective synthesis of isolasalocid A (**9**)[5] and lasalocid A (**10**),[6] which were isolated from *Streptomyces lasaliensis* as representatives of a growing class of naturally occurring polyether ionophore antibiotics. Kishi[3g] and Ireland[3h,i] achieved the total synthesis of **10** by means of their own methodologies. We report in this paper the stereoselective synthesis of **9** and **10**, describing the construction of the C rings (C_{18}-C_{24} subunits),[7] **11** and **12**, and the total synthesis of **9** and **10** *via* the construction of the B rings (C_{12}-C_{24} subunits) and the aldol condensation with the C_1-C_{11} aldehyde is reported in a subsequent paper.



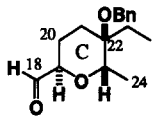
Isolasalocid A (9)



Lasalocid A (10)



11



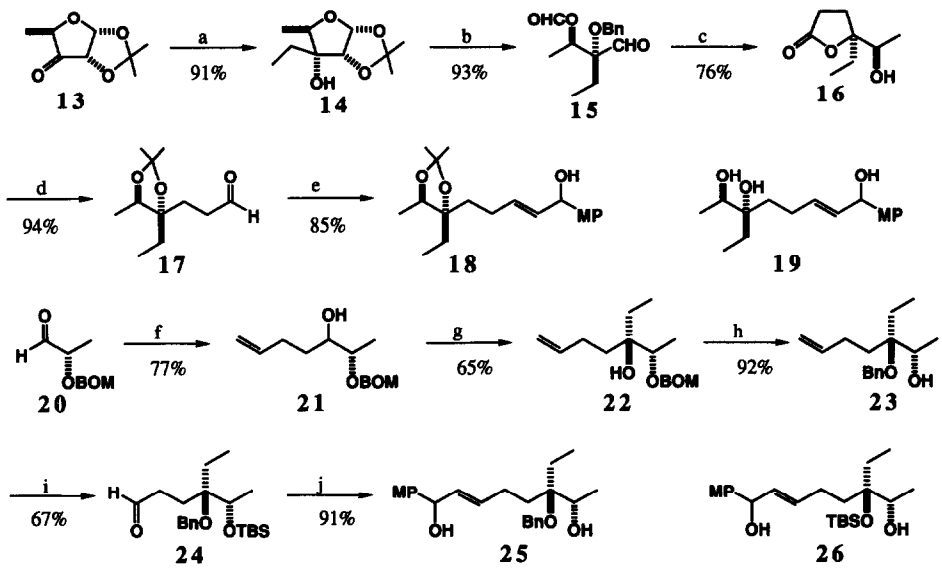
12

Synthesis of MP-allyl alcohols (18, 25)

When the ulose (**13**)[8] derived from D-glucose was treated with ethylmagnesium bromide, reduction of the carbonyl group mainly occurred and **14** was obtained in only 19% yield, whereas on treatment with vinylmagnesium bromide, addition of the Grignard reagent readily occurred stereoselectively to give the tertiary alcohol in excellent yield. Hydrogenation of the vinyl group over palladium on charcoal (Pd-C) gave **14**, which was converted to the aldehyde (**15**) in the usual way, and then treated with a stabilized ylid to give the lactone (**16**). Reduction with lithium aluminum hydride ($LiAlH_4$), and subsequent protection of the 1,2-diol as an acetonide and oxidation with pyridinium chlorochromate (PCC) readily gave the aldehyde (**17**), which was subjected to Wittig-Horner reaction with a β-ketophosphonate, followed by the selective reduction of the carbonyl group with sodium borohydride ($NaBH_4$) in the presence of cerium chloride ($CeCl_3$), and the MP-allyl alcohol (**18**) was isolated in good yield. The overall yield from **13** to **18** *via* 12 steps was 51%.

The aldehyde (**20**)[9] was converted to the alcohol (**21**) by treatment with 3-butenylmagnesium bromide. Swern oxidation[10] of **21** gave a ketone, which was treated with ethylmagnesium bromide. A chelation-controlled addition of the Grignard reagent occurred stereoselectively[11] to give **22**, whose tertiary alcohol was protected with a benzyl group, and then the benzyloxymethyl (BOM) protecting group was removed to give **23**. After protection of the secondary alcohol with a *tert*-butyldimethylsilyl (TBS) group, the double bond was

cleaved to the aldehyde (**24**), which was readily converted to the other MP-allyl alcohol (**25**). The overall yield from **20** to **25** *via* 11 steps was 28%.



(a) 1) CH_2=CHMgBr, THF, -20°C (91%); 2) H_2, 10%Pd/C, AcOEt, rt (100%) (b) 1) NaH, BnCl, DMF, rt (97%); 2) 4N HCl-THF (1 : 2), rt (99%); 3) $Pb(OAc)_4$, benzene, rt (97%) (c) 1) Ph_3P=$CHCO_2Me$, 1,2-dichloroethane, reflux (83%); 2) H_2, 10%Pd/C, AcOEt, rt, then K_2CO_3 (97%) (d) 1) $LiAlH_4$, Et_2O, 0°C (100%); 2) $Me_2C(OMe)_2$, CSA, benzene, rt (100%); 3) PCC, 3A-MS, CH_2Cl_2, rt (94%) (e) 1) NaH, $(MeO)_2P(O)CH_2COMP$, THF, 0°C (85%); 2) $NaBH_4$, $CeCl_3$, MeOH, 0°C (100%) (f) CH_2=$CHCH_2CH_2MgBr$, THF, 0°C (77%) (g) 1) Swern Oxid. (84%); 2) EtMgBr, THF, 0°C (77%) (h) 1) NaH, BnBr, DMF, rt (100%); 2) 4N HCl-THF (1 : 2), 45–60°C (92%) (i) 1) TBSCl, imidazole, DMF, 80°C (100%); 2) OsO_4, NMO, acetone-H_2O (4 : 1) (75%); 3) $NaIO_4$, MeOH (89%) (j) 1) NaH, $(MeO)_2P(O)CH_2COMP$, THF, 0°C (92%); 2) $NaBH_4$, $CeCl_3$, MeOH, 0°C (99%); 3) $^nBu_4NF$, THF, rt (100%)

Scheme 2

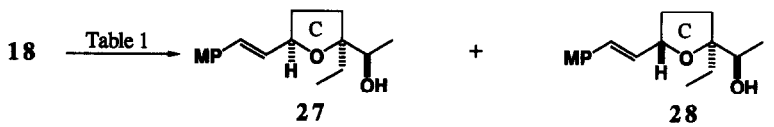
Synthesis of the C_{18}-C_{24} subunit (11) of isolasalocid A (9)

The MP-allyl alcohol (**18**) was readily cyclized to the corresponding THF (**27**, **28**) by treatment with either a protonic acid or Lewis acid in various solvents, and the reactivity and stereoselectivity of the cyclization varied markedly with reaction conditions (Table 1). When **18** was treated with a catalytic amount of *d*-camphorsulfonic acid (CSA) in benzene for 1 hour at room temperature, a 99:1 mixture of the undesired THF (**28**) and the desired THF (**27**) was isolated in 60% yield (entry 1). The yield of the cyclization reaction was improved in THF to 82% (entry 2). In dichloromethane, the cyclization proceeded quite rapidly and efficiently (entry 3, 4). In an initial stage, **28** was detected almost as a single product (entry 3), which came fairly rapidly to equilibrium with **27** (entry 4). The cyclization in methanol gave almost the same result (entry 5). A little slower reaction proceeded in tetrahydrofuran with hydrochloric acid (entry 6). Nonstereoselective cyclization was observed in the case of the triol (**19**) to give a 1.5:1 mixture of **28** and **27**. Therefore, it is obvious that the initial cyclization

of **18** was kinetically controlled by the steric effect between the isopropylidene group and the *p*-methoxystyryl group as shown in Scheme 4.

Some Lewis acids were also effective for the cyclization (entry 7-10). Among many Lewis acids tested, zinc bromide ($ZnBr_2$) was the most effective (entry 9,10). The main product was, unfortunately, still the undesired **28**, which had the wrong configuration at the C_{19} position, but this problem was easily solved by epimerization.

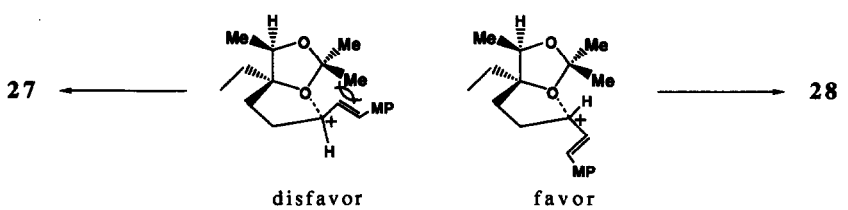
The *p*-methoxystyryl group of **28** was oxidized with osmium tetroxide (OsO_4), and the resulting diol was cleaved by periodate oxidation to give an aldehyde, which was treated with potassium hydroxide in methanol. Epimerization at the C_{19} position occurred smoothly and the cyclic hemiacetal (**29**) was obtained in good yield.



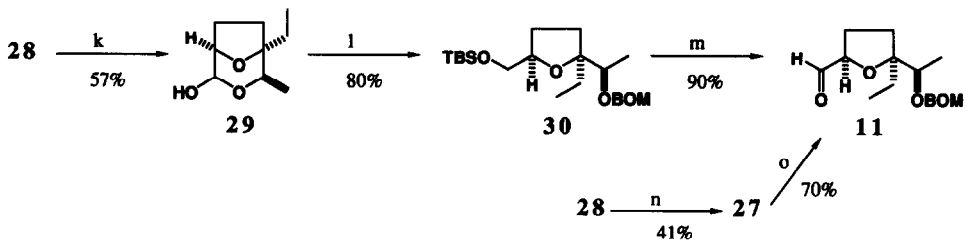
Scheme 3

Table 1. Acid-Catalyzed Cyclization of **18** at room temperature

entry	catalyst	solvent	time (hr)	yield (%)	ratio **27**: **28**
1	CSA	benzene	1	60	1.0 : 99
2	CSA	THF	1	82	1.0 : 99
3	CSA	CH_2Cl_2	0.33	95	1.0 : 99
4	CSA	CH_2Cl_2	1	89	1.0 : 2.1
5	CSA	MeOH	1	86	1.0 : 2.3
6	4N HCl	THF	1.5	91	1.0 : 10
7	$HgBr_2$	CH_2Cl_2	3	36	1.0 : 1.0
8	$ZnCl_2$	CH_2Cl_2	3	78	1.0 : 1.6
9	$ZnBr_2$	CH_2Cl_2	3	96	1.0 : 1.7
10	$ZnBr_2$	CH_2Cl_2	24	99	1.0 : 1.5



Scheme 4



(k) 1) OsO_4, NMO, H_2O-acetone (1 : 2), rt (81%); 2) $NaIO_4$, MeOH, rt (96%); 3) KOH, MeOH, rt (73%) (l) 1) $LiAlH_4$, Et_2O, 0°C (100%); 2) TBSCl, imidazole, 0°C, CH_2Cl_2 (93%); 3) BOMCl, $^iPr_2NEt$, CH_2Cl_2, rt (86%) (m) 1) 1N HCl-THF (1 : 5), rt (97%); 2) Swern Oxid. (93%) (n) 1) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt; 2) CSA, CH_2Cl_2, rt; 3) $LiAlH_4$, Et_2O, 0°C; 4) separation (41% via 3 steps) (o) 1) BOMCl, $^iPr_2NEt$, CH_2Cl_2, rt (100%); 2) OsO_4, NMO, H_2O-acetone (1 : 6) (82%); 3) $NaIO_4$, MeOH, rt (85% via 3 steps)

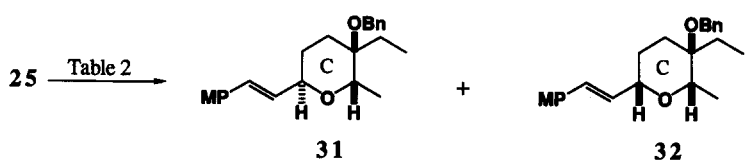
Scheme 5

This hemiacetal (**29**) was readily converted to the C_{18}-C_{24} subunit (**11**) *via* a series of five conventional reactions; reduction with $LiAlH_4$, protection of the C_{18} primary alcohol with a TBS group, protection of the C_{23} secondary alcohol with a BOM group, removal of the TBS group with hydrochloric acid, and Swern oxidation.

Alternatively, **27** was obtained from **28** by an acid-catalyzed equilibration at the C_{19} position, namely, the C_{23} acetate of **28** was treated with CSA at room temperature for 1 day. Removal of the acetyl group with $LiAlH_4$ gave a 1:1.4 mixture of **27** and **28**, which were readily separated by silica gel chromatography. The secondary alcohol of **27** was protected with a BOM group, and then oxidation with OsO_4, followed by periodate oxidation gave **11** in good yield.

Synthesis of the C_{18}-C_{24} subunit (12) of lasalocid A (10)

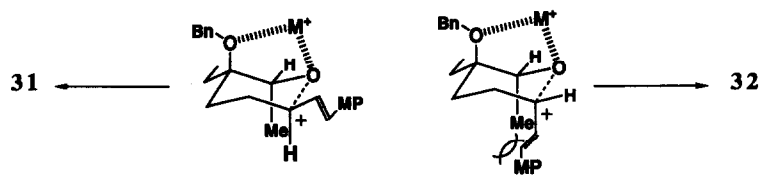
The results of cyclization of **25** are summarized in Table 2. The desired THP (**31**) was mainly obtained from **25** by a brief treatment with CSA, but both the yield and selectivity were inadequate (entry 1). At low temperature the yield was somewhat improved (entry 2). Since a prolonged acid treatment, however, caused the main kinetic product (**31**) to change gradually into the undesired THP (**32**); the ratio of **31** to **32** was reversed within several hours (entry 5), and after two days it was 1:4.3 (entry 6). It was therefore hardly possible to get **31** selectively by the protonic acid treatment.



Scheme 6

Table 2. Acid-Catalyzed Cyclization of **25**

entry	catalyst	solvent	temperature	time	yield (%)	ratio **31**:**32**
1	CSA	CH_2Cl_2	rt	3 min	54	4.4 : 1.0
2	CSA	CH_2Cl_2	-60°C	5 hr	67	4.3 : 1.0
3	CSA	CH_2Cl_2	rt	10 min	78	2.0 : 1.0
4	4N HCl	THF	rt	5 min	79	1.7 : 1.0
5	CSA	CH_2Cl_2	rt	12 hr	78	1.0 : 3.3
6	CSA	CH_2Cl_2	rt	2 day	60	1.0 : 4.3
7	CSA	toluene	100°C	1 day	55	1.0 : 6.2
8	$ZnBr_2$	CH_2Cl_2	rt	25 min	77	4.5 : 1.0
9	$ZnBr_2$	CH_2Cl_2	rt	12 hr	85	3.8 : 1.0
10	$ZnBr_2$	CH_2Cl_2	-20°C	1.5hr	79	14 : 1.0



Scheme 7

On treatment with $ZnBr_2$ instead of CSA for a short time, similarly **25** gave mainly **31** (entry 8). When **25** was treated with $ZnBr_2$ for a long time, **31** was still the main product (entry 9), in contrast to the cyclization with CSA. The best result to get **31** selectively was achieved at low temperature (entry 10).

It is obvious that **32** is thermodynamically more stable than **31**, which was nevertheless the main product in the cyclization with $ZnBr_2$ not only under kinetic conditions but also under thermodynamic conditions. This can be clearly explained in terms of a chelation-controlled reaction with $ZnBr_2$ that mainly proceeded *via* a favorable intermediate as shown in Scheme 7. The cyclization of **26** having no chelating ability due to steric effect of bulky TBS group supported this mechanism; thus, when **26** was treated with $ZnBr_2$ under the same conditions as described in entry 10, the non-chelation controlled product (**33**) was mainly obtained with 24:1 stereoselectivity.

Finally, oxidative cleavage of the double bond of **31** by treatment with OsO_4 and then sodium periodate ($NaIO_4$) readlily gave the C_{18}-C_{24} subunit (**12**) of lasalocid A (**10**).

Scheme 8

The total synthesis of isolasalocid A (**9**) and lasalocid A (**10**) *via* construction of the corresponding B rings is reported in the subsequent paper.

Experimental

5-Deoxy-3-*C*-ethyl-1,2-*O*-(1-methylethylidene)-α-D-ribofuranose (14)

A solution of the ulose (**13**) (9.49g, 55mmol) in THF (25ml) was added dropwise to a stirred solution of the Grignard reagent, prepared from Mg (2.43g, 100mmol), $(CH_2Br)_2$ (0.03ml), and vinyl bromide (7.0ml, 99mmol) in THF (75ml), at 0°C. After being stirred overnight at room temperature, the reaction mixture was poured into aqueous NH_4Cl with crushed ice, and extracted with ether. The extract was dried over $MgSO_4$, and evaporated. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 3:1) to give 5-deoxy-1.2-*O*-(1-methylethylidene)-3-*C*-vinyl-α-D-ribofuranose as colorless prisms (10.1g, 91%). mp 77-78°C. IR (Nujol) ν (cm^{-1}): 3450. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (d, 3H, *J*=6.5Hz), 1.36 (s, 3H), 1.60 (s, 3H), 2.61 (d, 1H, *J*=1.0Hz), 3.97 (q, 1H, *J*=6.5Hz), 4.23 (d, 1H, *J*=4.0Hz), 5.31 (dd, 1H, *J*=2.5, 10.5Hz), 5.46 (dd, 1H, *J*=3.0, 17.5Hz), 5.77 (ddd, 1H, *J*=1.0, 10.0, 17.5Hz), 5.81 (d, 1H, *J*=4.0Hz). EI-MS *m/z* (%): 185 (M^+-15, 0.9), 125 (8.5), 98 (100), 97 (74), 84 (60), 59 (97). *Anal* Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.82; H, 7.92.

A stirred solution of the above olefin (14.7g, 73.5mmol) in EtOAc (50ml) was hydrogenated over 10% Pd-C (2.1g) for 2 hr. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo*. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 7:1) to give **14** as colorless needles (15.2g, 100%). mp 79.5-80.5°C. $[\alpha]_D^{18}$ +20° (c=0.4, $CHCl_3$). IR (Nujol) ν (cm^{-1}): 3450. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (t, 3H, *J*=7.0Hz), 1.19 (d, 3H, *J*=6.5Hz), 1.37 (s, 3H), 1.57 (s, 3H), 1.53-1.72 (m, 2H), 2.46 (d, 1H, *J*=1.5Hz), 3.91 (q, 1H, *J*=6.5Hz), 4.29 (d, 1H, *J*=4.0Hz), 5.72 (d, 1H, *J*=4.0Hz). EI-MS *m/z* (%): 187 (M^+-15, 1.0), 144 (9.0), 129 (11), 127 (15), 100 (74), 86 (29), 71 (100), 59 (96). HR-MS *m/z* Calcd for $C_9H_{15}O_4$ (M^+-15): 187.09713. Found: 187.09826. *Anal* Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.82; H, 7.92.

(2*R*,3*R*)-Benzyloxy-2-ethyl-formyloxybutanal (15)

BnCl (10ml, 87mmol) and a solution of **14** (10.7g, 53mmol) in DMF (50ml) were successively added dropwise to a stirred suspension of NaH [60% oil dispersion (3.98g, 99mmol), washed with *n*-hexane] in DMF (100ml) at room temperature. After 7 hr, Et_2NH (12ml) was added, and the stirring was continued for 5 hr. The mixture was poured into aqueous NH_4Cl with crushed ice, and extracted with CH_2Cl_2. The extract was washed with 2N HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 9:1) to give 3-*O*-benzyl-5-deoxy-3-*C*-ethyl-1,2-*O*-(1-methylethylidene)-α-D-ribofuranose as a colorless oil (15.1g, 97%). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (t, 3H, *J*=7.5Hz), 1.26 (d, 3H, *J*=7.5Hz), 1.36 (s, 3H), 1.61 (s, 3H), 1.45-1.60 (m, 2H), 4.31 (q, 1H, *J*=7.5Hz), 4.42 (d, 1H, *J*=4.0Hz), 4.55 (d, 1H, *J*=12.0Hz), 4.68 (d, 1H, *J*=12.0Hz), 5.69 (d, 1H, *J*=4.0Hz), 7.25-7.41 (m, 5H). EI-MS *m/z* (%): 277 (M^+-15, 0.7), 234 (1.0), 216 (0.9), 190 (2.3), 157 (3.9), 143 (12), 91 (100). HR-MS *m/z* Calcd for $C_{16}H_{21}O_4$ (M^+-15): 277.14411. Found: 277.14342. *Anal* Calcd for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 59.59; H, 8.97.

4N HCl (120ml) was added to a stirred solution of the above benzyl ether (12.6g, 43.2mmol) in THF (240ml) at room temperature. After 24 hr, the reaction mixture was neutralized with 4N NaOH, concentrated *in*

vacuo, and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 3:1) to give 3-*O*-benzyl-5-deoxy-3-*C*-ethyl-α-D-ribofuranose as a pale yellow oil (10.8g, 99%). ^{1}H-NMR ($CDCl_3$) δ: 1.06 (t, 6/5H, *J*=7.5Hz), 1.10 (t, 9/5H, *J*=7.5Hz), 1.25 (d, 9/5H, *J*=7.0Hz), 1.32 (d, 6/5H, *J*=7.0Hz), 1.39-2.14 (m, 2H), 3.10 (d, 2/5H, *J*=4.0Hz), 3.11 (dd, 3/5H, *J*=4.5, 11.0Hz), 3.89 (dd, 2/5H, *J*=7.0, 8.0Hz), 3.93 (dd, 3/5H, *J*=6.5, 9.5Hz), 4.27-4.59 (m, 1H), 5.12-5.27 (m, 1H), 7.34 (s, 5H). EI-MS *m/z* (%): 234 (M^+-18, 0.4), 216 (M^+-36, 0.3), 207 (0.6), 205 (0.7), 190 (1.5), 170 (1.0), 149 (2.8), 144 (3.7), 143 (4.0), 133 (6.8), 91 (100), 57 (77).

$Pb(OAc)_4$ (20g, 45mmol) was added to a stirred solution of the above diol (5.5g, 21.8mmol) in dry benzene (50ml) at room temperature under argon. After 30 min, the reaction mixture was filtered, and the filtrate was evaporated *in vacuo*. The residue was dissolved in *n*-hexane, insoluble materials were removed by filtration, and filtrate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 2:1) to give **15** as a colorless oil (5.3g, 97%). IR (neat) ν (cm^{-1}): 1740, 1720. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (t, 3H, *J*=7.5Hz), 1.28 (d, 3H, *J*=6.5Hz), 1.91 (q, 2H, *J*=7.0Hz), 4.52 (d, 1H, *J*=11.0Hz), 4.70 (d, 1H, *J*=11.0Hz), 5.47 (q, 1H, *J*=6.5Hz), 7.36 (s, 5H), 8.10 (s, 1H). 9.70 (s, 1H). EI-MS *m/z* (%): 221 (M^+-29, 5.8), 105 (4.7), 91 (100).

(4*S*,5*R*)-4,5-Dihydroxy-4-ethylhexanoic Acid 1,4-Lactone (16)

Methoxycarbonylmethylenetriphenylphosphorane (27g, 80mmol) was added to a stirred solution of **15** (15g, 60mmol) in $(CH_2Cl)_2$ (200ml) at 60-70°C. After 12 hr, the phosphorane (11g) was added, the stirring was continued for another 12 hr, and then the reaction mixture was concentrated *in vacuo*. The residue was taken up in *n*-hexane, insoluble materials were filtered off, and the filtrate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 8:1) to give the recovered **15** (1.0g, 6.7%) and methyl (4*S*,5*R*,2*E*)-4-benzyloxy-4-ethyl-5-formyloxy-2-hexenoate as a colorless oil (14.2g, 77%; 83% based on the consumed **15**). $[\alpha]_D^{21}$ 39° (c=1.73, $CHCl_3$). IR (neat) ν (cm^{-1}): 1720, 1650, 1630. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (t, 3H, *J*=7.5Hz), 1.27 (d, 3H, *J*=6.5Hz), 1.68 (dq, 1H, *J*=15.0, 7.5Hz), 1.99 (dq, 1H, *J*=15.0, 7.5Hz), 3.76 (s, H), 4.41 (d, 1H, *J*=11.5Hz), 4.58 (d, 1H, *J*=11.5Hz), 5.31 (q, 1H, *J*=6.5Hz), 6.16 (d, 1H, *J*=16.0Hz), 6.89 (d, 1H, *J*=16.0Hz), 7.33 (s, 5H), 8.12 (s, 1H). EI-MS *m/z* (%): 233 (M^+-73, 3.4), 143 (5.6), 129 (11), 91 (100). HR-MS *m/z* Calcd for $C_{14}H_{17}O_3$ (M^+-73): 233.11787. Found: 233.11622.

A stirred solution of the above unsaturated ester (4.9g, 16mmol) in MeOH (200ml) was hydrogenated over 10% Pd-C (1.56g). After 24 hr, K_2CO_3 (1g) was added, and the stirring was continued for 1 hr. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 4:1-2:1) to give **16** as a colorless oil. (44g, 97%). $[\alpha]_D^{21}$ -19° (c=1.92, $CHCl_3$). IR (neat) ν (cm^{-1}): 3450, 1760. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (t, 3H, *J*=7.5Hz), 1.16 (d, 3H, *J*=6.5Hz), 1.68 (q, 2H, *J*=7.5Hz), 1.76-1.93 (m, 1H), 1.55-2.06 (br, 1H), 2.32 (dd, 1H, *J*=7.5, 10.5Hz), 2.47-2.72 (m, 2H), 4.01 (q, 1H, *J*=6.5Hz). EI-MS *m/z* (%): 159 (M^++1, 0.1), 129 (M^+-29, 5.2), 114 (11), 113 (100), 95 (11), 85 (12). HR-MS *m/z* Calcd for $C_6H_9O_3$ (M^+-29): 129. 05523. Found: 129. 05520.

3-[(4*S*,5*R*)-(4-Ethyl-2,2,5-trimethyl-1,3-dioxolan)-4-yl]propanal (17)

A solution of **16** (2.44g, 15.4mmol) in ether (10ml) was added dropwise to a stirred suspension of $LiAlH_4$ (1.17g, 30.8mmol) in ether (30ml) at 0°C. After 5 hr, a mixture of ether and MeOH (10:1) was carefully added, then H_2O (1.2ml), 15% NaOH (1.2ml), and H_2O were successively added, stirring was continued for 8 hr, and the mixture was extracted with ether and then with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (CH_2Cl_2-MeOH

50:1-15:1) to give (4*S*,5*R*)-4-ethyl-1,4,5-hexanetriol as a colorless oil (2.5g, 100%). IR (neat) ν (cm^{-1}): 3400. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (t, 3H, *J*=7.5Hz), 1.17 (d, 3H, *J*=6.5Hz), 1.45-1.75 (m, 6H), 2.00-2.60 (br, 3H), 3.61-3.83 (m, 3H). EI-MS *m/z* (%): 145 (M^+-17, 0.2), 117 (11), 115 (13), 103 (13), 99 (56), 85 (7.7), 69 (9.0), 57 (100).

2,2-Dimethoxypropane (1ml) and CSA (20mg) were added to a stirred solution of the above triol (0.46g, 2.84mmol) at room temperature. After 3 hr, Et_3N (0.02ml) was added, and the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 3:1) to give 3-[(4*S*,5*R*)-4-ethyl-2,2,5-trimethyl-1,3-dioxolan-4-yl]propanol as a colorless oil (0.58g, 100%). IR (neat) ν (cm^{-1}): 3450. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (t, 3H, *J*=7.5Hz), 1.13 (d, 3H, *J*=6.5Hz), 1.36 (s, 3H), 1.44 (s, 3H), 1.48-1.86 (m, 6H), 2.07 (br, 1H), 3.67 (m, 2H), 4.06 (q, 1H, *J*=6.5Hz). ^{13}C-NMR ($CDCl_3$) δ: 8.34 (q). 14.70 (q). 26.58 (t), 26.78 (q), 28.12 (t), 28.41 (q), 29.37 (t), 63.38 (t), 77.13 (d), 83.86 (s), 106.40 (s). EI-MS *m/z* (%): 187 (M^+-15, 8.2), 173 (0.5), 143 (32), 137 (42), 109 (17), 86 (76), 58 (86), 43 (100).

PCC (4.26g, 19.8mmol) was added to a vigorously stirred suspension of the above alcohol (1.6g, 7.92mmol), powdered molecular sieves 3A (4.26g), and anhydrous NaOAc (0.39g, 4.76mmol) at room temperature. After 30 min, the reaction mixture was passed through a short silica gel column (*n*-hexane-EtOAc 3:1) to give **17** as a colorless oil (1.5g, 94%). $[\alpha]_D^{18}$ -14° (c=1.2, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (t, 3H, *J*=7.5Hz), 1.25 (d, 3H, *J*=6.5Hz), 1.35 (s, 3H), 1.40 (s, 3H), 1.46-2.07 (m, 4H), 2.45-2.68 (m, 2H), 4.07 (q, 1H, *J*=6.5Hz), 9.84 (t, 1H, *J*=1.5Hz). EI-MS *m/z* (%): 201 (M^++1, 0.6), 185 (22), 143 (24), 125 (24), 85 (60), 58 (74), 43 (100). HR-MS *m/z* Calcd for $C_{11}H_{21}O_3$ (MH^+): 201.1485. Found: 201.1485.

(2*E*)-5-[(4*S*,5*R*)-4-Ethyl-2,2,5-trimethyl-1,3-dioxolan-4-yl)]-1-(4-methoxyphenyl)pent-2-en-1-ol (18)

Dimethyl (4-methoxyphenyl)carbonylmethanephosphonate (1.88g, 7.04mmol) was added to a stirred suspension of NaH [60% dispersion (0.27g, 6.75mmol), washed with *n*-hexane] in THF (20ml) at 0°C. After 20 min at room temperature, a solution of **17** (0.78g, 3.9mmol) was added dropwise, and stirring was continued for 2 hr. After addition of aqueous NH_4Cl, the mixture was extracted with ether. The extract was dried over $MgSO_4$, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 8:1) to give (2*E*)-5-[(4*S*,5*R*)-4-ethyl-2,2,5-trimethyl-1,3-dioxolan-4-yl)]-1-(4-methoxyphenyl)-pent-2-en-1-one as a colorless oil (1.1g, 85%). IR (neat) ν (cm^{-1}): 1670, 1620, 1600. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (t, 3H, *J*=7.5Hz), 1.24 (d, 3H, *J*=6.5Hz), 1.37 (s, 3H), 1.44 (s, 3H), 1.48-1.59 (m, 1H), 1.64 (q, 2H, *J*=7.5Hz), 1.62-1.81 (m, 1H), 2.22-2.56 (m, 2H), 3.88 (s, 3H), 4.06 (q, 1H, *J*=6.5Hz), 6.91 (d, 1H, *J*=14.0Hz), 6.95 (d, 2H, *J*=9.0Hz), 7.09 (dt, 1H, *J*=14.0, 7.0Hz), 7.95 (d, 2H, *J*=9.0Hz), EI-MS *m/z* (%): 332 (M^+, 0.9), 317 (M^+-15, 5.2), 275 (6.8), 274 (7.9), 257 (5.6), 256 (4.0), 202 (7.0), 189 (41), 135 (100).

The above enone (1.42g, 4.28mmol) and then $NaBH_4$ (0.32g, 8.46mmol) were added to a stirred 0.4M solution of $CeCl_3$ in MeOH (10ml) at 0°C. After 10 min, H_2O and ether were added, and the mixture was extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 8:1) to give **18** as a colorless oil (1.43g, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (t, 3H, *J*=7.5Hz), 1.20 (d, 3H, *J*=6.5Hz), 1.34 (s, 3H), 1.40 (s, 3H), 1.33-1.45 (m, 2H), 1.53-1.68 (m, 2H), 1.88 (br, 1H), 1.96-2.23 (m, 2H), 3.80 (s, 3H), 4.01 (q, 1H, *J*=6.5Hz), 5.12 (d, 1H, *J*=5.5Hz), 5.68 (dd, 1H, *J*=5.5, 15.0Hz), 5.75-5.86 (m, 1H), 6.88 (d, 2H,

J=8.5Hz), 7.29 (d, 2H, *J*=9.0Hz). EI-MS *m/z* (%): 334 (M^+, 0.3), 319 (M^+-15, 1.3), 316 (M^+-18, 0.9), 276 (6.9), 258 (13), 241 (9.8), 173 (51), 143 (100), 135 (87), 121 (74), 86 (82), 85 (78).

(1*RS*,6*S*,7*R*)-6-Ethyl-1-(4-methoxyphenyl)octane-1,6,7-triol (19)

(1*RS*,6*S*,7*R*)-6,7-di-*tert*-butyldimethylsilyloxy-6-ethyl-1-(4-methoxyphenyl)octan-1-ol (596mg, 1.14mmol), derived from **16** (389mg, 2.46mmol) *via* (4*S*,5*R*)-4,5-di-*tert*-butyldimethylsilyloxy-5-ethylhexanal (766mg 1.97mmol) in 46% overall yield according to a method quite similar to that described for the preparation of **18**, was treated with *n*-Bu_4NF (9.1ml of 1M solution in THF, 9.1mmol) in THF (13ml) and DMF (1.3ml) under heating at 60°C for 3 hr. The reaction mixture was diluted with ether (70ml), washed with H_2O and brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (EtOAc) to give **19** as a colorless oil (322mg, 96%). IR (neat) ν (cm^{-1}): 3500. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (t, 3H, *J*=7.5Hz), 0.95 (d, 1.5H, *J*=6.0Hz), 0.96 (d, 1.5H, *J*=6.0Hz), 1.26-1.64 (m, 7H), 1.93-2.02 (m, 1H), 2.14-2.21 (m, 1H), 3.35 (s, 3H), 3.48 (q, 1H, *J*=6.0Hz), 5.04 (d, 1H, *J*=4.5Hz), 5.67~5.75 (m, 2H), 6.87 (d, 2H, *J*=8.5Hz), 7.34 (d, 2H, *J*=8.5Hz). FAB-MS *m/z* (%): 276 (M^+-18, 31), 259 (18), 242 (79), 231 (23), 219 (11), 213 (13), 173 (36), 167 (16), 159 (22), 155 (21), 154 (100), 150 (26), 149 (52), 147 (16), 143 (23), 137 (52), 136 (64), 121 (44), 107 (26), 91 (23), 89 (25). HR-MS *m/z* Calcd for $C_{17}H_{24}O_3$ (M^+-18): 276.1719. Found: 172.1719.

(2*S*,3*RS*)-2-Benzyloxymethoxyhept-6-en-2-ol (21)

A solution of **20** (4.8g, 24.7mmol) in THF (10ml) was added dropwise to a stirred solution of the Grignard reagent, prepared from Mg (2.48g, 0.1mol) and 4-bromobut-1-ene (12ml, 118mmol) in THF (200ml), at 0°C. After being stirred overnight, the reaction mixture was poured into aqueous NH_4Cl with crushed ice, and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 5:1) to give **21** as a colorless oil (4.75g, 77%). IR (neat) ν (cm^{-1}): 3600. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (d, 3H, *J*=6.0Hz), 1.44-1.67 (m, 2H), 2.09-2.36 (m, 2H), 2.58 (d, 1H, *J*=6.0Hz), 3.32-3.98 (m, 1H), 3.66 (q, 1H), 4.64 (s, 2H), 4.93 (m, 2H), 4.92-5.04 (m, 1H), 3.66 (q, 1H), 4.64 (s; 2H), 4.93 (m, 2H), 4.92-5.04 (m, 1H), 4.96-5.16 (m, 1H), 5.84 (ddt, 1H, *J*=10.0, 17.0, 6.5Hz), 7.34 (s, 5H). FAB-MS *m/z* (%): 251 (MH^+, 14), 244 (6.9), 233 (4.7), 219 (4.1), 197 (3.2), 185 (6.2), 154 (35), 149 (12) 143 (10), 138 (14), 137 (27), 136 (24) 107 (17), 91 (100), 77 (38), 67 (22) 57 (34). HR-MS *m/z* Calcd for $C_{15}H_{23}O_3$ (MH^+): 251.1641. Found: 251.1635.

(2*S*,3*R*)-2-Benzyloxymethoxy-3-ethylhept-6-en-3-ol (22)

DMSO (9.9ml) in CH_2Cl_2 (10ml) was added to a stirred solution of oxalyl chloride (4.45ml, 51mmol) in CH_2Cl_2 (80ml) at -78°C under argon. A solution of **21** (8.6g, 34.4mmol) in CH_2Cl_2 (10ml) was then added dropwise. After 1.5 hr at -78~-50°C, Et_3N (20.6ml) was added dropwise, and stirring was continued for 2 hr. CH_2Cl_2 and H_2O were added, and the CH_2Cl_2 layer was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 3:1) to give (2*S*)-2-benzyloxymethoxyhept-6-en-3-one as a colorless oil (7.07g, 84%). $[\alpha]_D^{18}$ -23° (c=1.04, $CHCl_3$). IR (neat) ν (cm^{-1}): 1720, 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (d, 3H, *J*=7.0Hz), 2.27-2.35 (m, 2H), 2.53-2.73 (m, 2H), 4.20 (q, 1H, *J*=6.5Hz), 4.63 (s, 2H), 4.77 (d, 1H, *J*=7.0Hz), 4.84 (d, 1H, *J*=7.0Hz), 4.97 (ddt, 1H, *J*=3.0, 10.5, 1.0Hz), 5.03 (ddt, 1H, *J*=3.5, 17.0, 2.0Hz), 5.79 (ddt, 1H, *J*=10.5, 17.0, 6.0Hz), 7.27-7.39 (m, 5H). EI-MS *m/z* (%): 165 (M^+-83, 1.7), 135 (12), 91 (100), 83 (23).

The above ketone (1.55g, 6.3mmol) was treated with EtMgBr, prepared from Mg (1.06g, 43.6mmol) and EtBr (3.0ml), in THF (310ml) at -78°C. Work-up as described for **14** gave **22** as a colorless oil (1.34g, 77%).

$[\alpha]_D^{18}$ +26° (c=0.61, $CHCl_3$). IR (neat) ν (cm^{-1}): 3550, 3400. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (t, 3H, *J*=7.5Hz), 1.18 (d, 3H, *J*=6.0Hz), 1.39-1.56 (m, 2H), 1.61-1.72 (m, 2H), 1.97-2.27 (m, 2H), 2.26-2.40 (br, 1H), 3.72 (q, 1H, *J*=6.0Hz), 4.62 (d, 1H, *J*=9.5Hz), 4.67 (d, 1H, *J*=9.5Hz), 4.81 (d, 1H, *J*=7.0Hz), 4.86 (d, 1H, *J*=7.0Hz), 4.95 (ddt, 1H, *J*=2.0, 10.5, 1.0Hz), 5.03 (ddt, 1H, *J*=3.5, 17.0, 1.5Hz), 5.84 (ddt, 1H, *J*=10.5, 17.0, 6.5Hz), 7.27-7.36 (s, 5H). FAB-MS *m/z* (%): 279 (MH^+, 10), 244 (5.7), 231 (5.5), 219 (4.0), 197 (4.3), 181 (4.8), 171 (17), 154 (31) 141 (24), 137 (22), 136 (24), 91 (100), 77 (15), 57 (19). HR-MS *m/z* Calcd for $C_{17}H_{27}O_3$ (MH^+): 279.1953. Found: 279.1960.

(2*S*,3*R*)-3-Benzyloxy-3-ethylhept-6-en-2-ol (23)

To a suspension of NaH (60% oil dispersion, 1,37g, 34.3mmol) in dry DMF (30ml) was slowly added dropwise the alcohol (**22**) (5.29g, 19mmol) in dry DMF (30ml) at room temperature. After being stirred for 2 hr, benzyl chloride (5.7ml, 48mmol) was added into the solution. After being stirred for 2 hr at room tamperature, the resulting mixture was poured into a cold aqueous NH_4Cl solution, and extracted with ether (100ml x 2). The extract was washed with H_2O and brine, and then dried over anhydrous $MgSO_4$. The organic solvent was evaporated under reduced pressure to leave an oil, which was chromatographed on a silica gel column (EtOAc - *n*-hexane 1 : 10) to give (5*R*,6*S*)-5-benzyloxy-6-benzyloxymethoxy-5-ethylhept-1-ene as a colorless oil (7.0g, 100%). $[\alpha]_D^{18}$ +28° (c=1.74, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (t, 3H, *J*=7.5Hz), 1.29 (d, 3H, *J*=6.0Hz), 1.62-1.85 (m, 4H), 2.06-2.20 (m, 2H), 3.86 (q, 1H, *J*=6.0Hz), 4.49 (d, 1H, *J*=11.5Hz), 4.61 (d, 1H, *J*=11.5Hz), 4.62 (d, 1H, *J*=12.0Hz), 4.67 (d, 1H, *J*=12.0Hz), 4.78 (d, 1H, *J*=7.0Hz), 4.86 (d, 1H, *J*=7.0Hz), 4.91-4.96 (m, 1H), 5.02 (ddt, 1H, *J*=2.0, 17.0, 1.5Hz), 5.84 (ddt, 1H, *J*=10.5, 17.0, 6.5Hz), 7.21-7.38 (m, 10H). EI-MS *m/z* (%): 247 (M^+-121, 0.1), 233 (0.1), 203 (16), 185 (3.2), 91 (100).

4N HCl (100ml) and MeOH (20ml) were added to a stirred solution of the above ether (7.05g, 19.1mmol) in THF (200ml). After 4 hr at 50°C, the reaction mixture was neutralized with $NaHCO_3$, and extracted with ether. The extract was dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 8:1) to give the recovered ether (1.31g) and **23** as a colorless oil (3.54g, 75%; 92% based on the consumed starting material). $[\alpha]_D^{18}$ +20° (c=0.81, $CHCl_3$). IR (neat) ν (cm^{-1}): 3520. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (t, 3H, *J*=7.5Hz), 1.21 (d, 3H, *J*=6.0Hz), 1.52-1.81 (m, 4H), 2.08-2.23 (m, 2H), 2.32-2.43 (m, 1H), 2.40-2.52 (br, 1H), 3.97 (q, 1H, *J*=6.5Hz), 4.44 (d, 1H, *J*=11.5Hz), 4.48 (d, 1H, *J*=11.0Hz), 4.92-4.96 (m, 1H), 5.03 (ddt, 1H, *J*=2.0, 17.0, 1.5Hz), 5.38 (ddt, 1H, *J*=10.5, 17.0, 6.5Hz), 7.27-7.36 (m, 5H). FAB-MS *m/z* (%): 249 (MH^+, 8.3), 244 (7.6), 231 (10), 219 (10), 203 (33), 154 (64), 137 (36), 136 (41), 91 (100), 89 (11), 77 (11) 43 (11). HR-MS *m/z* Calcd for $C_{16}H_{25}O_2$ (MH^+): 249.1848. Found: 249.1877

(4*R*,5*S*)-4-Benzyloxy-5-*tert*-butyldimethylsilyloxy-4-ethylhexanal (24)

Imidazole (3.5g, 51.5mmol) and TBS chloride (3.9g, 25.8mmol) were added to a stirred solution of **23** (3.2g, 12.9mmol) in DMF (40ml) at room temperature. After being heated at 80°C for 6 hr, the reaction mixture was cooled to room temperature, diluted with H_2O and ether, and then extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 12:1) to give (5*R*,6*S*)-5-benzyloxy-6-*tert*-butyldimethylsilyloxy-5-ethylhept-1-ene as a colorless oil (5.07g, 100%). $[\alpha]_D^{19}$ +12° (c=0.92, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.06 (s, 3H), 0.08 (s, 3H), 0.90 (t, 3H, *J*=7.5Hz), 1.24 (d, 3H, *J*=6.0Hz), 1.50-1.61 (m, 1H), 1.65-1.85 (m, 3H), 1.96-2.20 (m, 2H), 3.87 (q, 1H, *J*=6.0Hz), 4.48 (d, 1H, *J*=11.5Hz), 4.66 (d, 1H, *J*=11.5Hz), 4.90-4.97 (m, 1H), 4.97-5.07 (m, 1H), 5.84 (ddt, 1H, *J*=10.5, 17.0, 6.5Hz), 7.23-7.35 (m, 5H). EI-MS *m/z* (%): 333

(0.2), 305 (2.6), 263 (0.7), 213 (1.0), 203 (19), 159 (9.4), 91 (100). HR-MS *m/z* Calcd for $C_{20}H_{33}O_2Si$ (M^+-29): 333.22493. Found: 333.22327.

N-Methylmorpholine oxide (NMO) (3.65g, 27mmol) and OsO_4 (10mg) were added to a stirred solution of the above olefin (6.51g, 18mmol) in acetone (200ml) and H_2O (45ml) at room temperature. After 6 hr, $Na_2S_2O_4$, Celite, and H_2O were added, and stirring was continued overnight. The mixture was filtered, and the filtrate was adjusted to pH 7 with 2% H_2SO_4 and then concentrated *in vacuo*. The aqueous residue was extracted with CH_2Cl_2, and the extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 5:1) to give (2*RS*,5*R*,6*S*)-5-benzyloxy-6-*tert*-butyldimethylsilyloxy-5-ethyl-1, 2-heptanediol as a colorless oil (5.34g, 75%). IR (neat) ν (cm^{-1}): 3530, 3380. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (s, 3/2H), 0.07 (s, 3/2H), 0.09 (s, 3H), 0.90 (t, 3/2H, *J*=7.5Hz), 0.91 (s, 9H), 0.91 (t, 3/2H, *J*=7.5Hz), 1.25 (d, 3/2H, *J*=6.0Hz), 1.26 (d, 3/2H, *J*=6.0Hz), 1.39-1.69 (m, 3H), 1.70-1.97 (m, 5H), 3.40 (dd, 1/2H, *J*=3.5, 7.5Hz), 3.44 (dd, 1/2H, *J*=3.0, 7.5Hz), 3.59-3.74 (m, 2H), 3.86 (q, 1H, *J*=6.5Hz), 4.51 (d, 1H, *J*=11.5Hz), 4.73 (d, 1/2H, *J*=11.5Hz), 4.77 (d, 1/2H, *J*=11.5Hz), 7.25-7.33 (m, 5H). EI-MS *m/z* (%): 307 (M^+-89, 0.3), 259 (0.9), 257 (2), 231 (1.5), 219 (16), 129 (22), 91 (100).

$NaIO_4$ (5.69g, 26.6mmol) was added to a stirred solution of the above diol (5.27g, 13.3mmol) in MeOH (50ml) and H_2O (25ml) at room temperature. After 30 min, the reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. The aqueous residue was extracted with ether, then the extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 20:1) to give **24** as a colorless oil (4.28g, 89%). $[\alpha]_D^{19}$ +12° (c=1.10, $CHCl_3$). IR (neat) ν (cm^{-1}): 1710. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 0.91 (t, 3H, *J*=7.5Hz), 1.24 (d, 3H, *J*=6.0Hz), 1.60 (dq, 1H, *J*=14.5, 7.5Hz), 1.65 (dq, 1H, *J*=14.5, 7.5Hz), 1.76-2.00 (m, 2H), 2.47 (dddd, 1H, *J*=1.5, 5.5, 9.5, 17.5Hz), 2.64 (dddd, 1H, *J*=2.0, 6.0, 10.5, 17.5Hz), 3.88 (q, 1H, *J*=6.5Hz), 4.43 (d, 1H, *J*=11.5Hz), 4.63 (d, 1H, *J*=11.5Hz), 7.21-7.33 (m, 5H), 9.76 (dd, 1H, *J*=1.5, 2.0Hz). EI-MS *m/z* (%): 307 (M^+-57, 0.4), 221 (1.4), 215 (0.9), 205 (1.2), 159 (8.5), 113 (8.9), 91 (100). HR-MS *m/z* Calcd for $C_{17}H_{27}O_3Si$ (M^+-57): 307.17290. Found: 307.17453.

(1*RS*,2*E*,6*R*,7*S*)-6-Benzyloxy-6-ethyl-1-(4-methoxyphenyl)oct-2-ene-1,7-diol (25)

A solution of **24** (4.28g, 11.8mmol) in THF (20ml) was added dropwise to a stirred solution of the ketophosphonate reagent, prepared from NaH (60% oil dispersion, 0.58g, 14.5mmol) and dimethyl (4-methoxyphenyl)carbonylmethanephosphonate (3.48g, 15.4mmol). After 6 hr at room temperature, work-up as described for **18** gave the recovered **24** (0.77g, 18%) and (2*E*,6*R*,7*S*)-6-benzyloxy-7-*tert*-butyldimethylsilyloxy-6-ethyl-1-(4-methoxyphenyl)oct-2-en-1-one as a colorless oil (4.39g, 75%; 92% based on the consumed **24**). $[\alpha]_D^{19}$ +11° (c=0.85, $CHCl_3$). IR (neat) ν (cm^{-1}): 1670. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 0.95 (t, 3H, *J*=7.5Hz), 1.26 (d, 3H, *J*=6.0Hz), 1.59-1.96 (m, 4H), 2.20-2.55 (m, 2H), 3.88 (s, 3H), 3.90 (q, 1H, *J*=6.0Hz), 4.49 (d, 1H, *J*=11.5Hz), 4.66 (d, 1H, *J*=11.5Hz), 6.88 (d, 1H, *J*=15.5Hz), 6.98 (d, 2H, *J*=9.0Hz), 7.07 (dt, 1H, *J*=15.5, 6.5Hz), 7.24-7.35 (m, 5H), 7.93 (d, 2H, *J*=9.0Hz). EI-MS *m/z* (%): 467 (0.1), 439 (2.0), 361 (1.0), 337 (16), 159 (13), 139 (28), 135 (37), 91 (100). HR-MS *m/z* Calcd for $C_{26}H_{35}O_4Si$ (M^+-57): 439.23042. Found: 439.22882.

The above enone (4.33g, 8.7mmol) was treated with $NaBH_4$ (0.66g, 17mmol) and 0.4M $CeCl_3$ in MeOH (60ml) under cooling with ice bath. After 10 min, H_2O and ether (ca. 200ml) were added into the resulting mixture, and the mixture was extracted with ether. The organic layer was washed with brine and then dried

over anhydrous $MgSO_4$, and evaporated under reduced pressure to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 1 : 8) to give (1*RS*,2*E*,6*R*,7*S*)-6-benzyloxy-7-*tert*-butyldimethylsilyloxy-6-ethyl-1-(4-methoxyphenyl)oct-2-en-1-ol as a colorless oil (4.3g, 99%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 0.91 (t, 3H, *J*=7.5Hz), 1.23 (d, 3H, *J*=6.0Hz), 1.44-1.84 (m, 5H), 1.97-2.23 (m, 2H), 3.80 (s, 3H), 3.85 (q, 1H, *J*=6.5Hz), 4.47 (d, 1H, *J*=11.5Hz), 4.65 (d, 1H, *J*=11.5Hz), 5.11 (brd, 1H, *J*=6.0Hz), 5.62-6.01 (m, 2H), 6.88 (d, 2H, *J*=9.0Hz). 7.28 (d, 2H, *J*=8.5Hz), 7.20-7.33 (m, 5H). EI-MS *m/z* (%): 480 (M^+-18, 0.4), 423 (1.0), 333 (1.4), 321 (6.2), 231 (26), 173 (28), 91 (100). HR-MS *m/z* Calcd for $C_{30}H_{44}O_3Si$ (M^+-18): 480.30591. Found: 480.30583.

1M THF solution of *n*-Bu_4NF (30ml) was added to a stirred solution of the above TBS compound (4.27g, 8.6mmol) at room temperature. After being stirred at 60°C for 7 hr, the reaction mixture was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 5:1) to give **25** as a colorless oil (3.3g, 100%). IR (neat) ν (cm^{-1}): 3425. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (t, 3Hx2/3, *J*=7.5Hz), 1.00 (t, 3Hx1/3, *J*=7.5Hz), 1.25 (d, 3Hx1/3, *J*=6.5Hz), 1.32 (d, 3Hx2/3, *J*=6.0Hz), 1.36-1.69 (m, 4H), 1.69-2.18 (m, 4H), 3.97 (q, 1Hx1/3, *J*=6.5Hz), 3.80 (s, 3H), 4.01-4.08 (m, 1Hx2/3), 4.16 (q, 1Hx2/3, *J*=6.0Hz), 4.27-4.34 (m, 1Hx2/3), 4.37 (d, 1Hx2/3, *J*=11.0Hz), 4.50 (d, 1Hx2/3, *J*=11.0Hz), 4.51 (d, 1Hx1/3, *J*=11.0Hz), 4.60 (d, 1Hx1/3, *J*=11.0Hz), 6.10 (dd, 1Hx1/3, *J*=6.5, 16.0Hz), 6.13 (dd, 1Hx2/3, *J*=6.0, 16.0Hz), 6.54 (brd, 1H, *J*=16.0Hz), 6.84 (d, 2H, *J*=8.5Hz), 7.23-7.45 (m, 5H), 7.32 (d, 2H, *J*=8.5Hz). EI-MS *m/z* (%): 366 (M^+-18, 5.0), 275 (17), 260 (17), 258 (19), 231 (20), 213 (31), 161 (49), 160 (37), 159 (51), 121 (42), 91 (100). HR-MS *m/z* Calcd for $C_{24}H_{30}O_3$ (M^+-18): 366.21946. Found: 366.21871.

(2*S*,5*S*)-2-Ethyl-2-[(1*R*)-1-hydroxyethyl]-5-[(1*E*)-2-(4-methoxyphenyl)ethenyl]-tetrahydrofuran (28)

CSA (15mg, 0.065mmol) was added to a stirred solution of **19** (0.72g, 2.16mmol) in CH_2Cl_2 (6ml) at room temperature. After 20 min, the reaction mixture was neutralized with Et_3N (0.05ml), and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 10:1) to give **28** as a colorless oil (0.57g, 95%). $[\alpha]_D^{15}$ -73° (c=0.97, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.97 (t, 3H, *J*=7.5Hz), 1.12 (d, 3H, *J*=6.0Hz), 1.49 (dq, 1H, *J*=14.0, 7.5Hz), 1.58 (dq, 1H, *J*=14.0, 7.5Hz), 1.57-1.65 (m, 1H), 1.71-1.86 (m, 1H), 2.06-2.15 (m, 1H), 2.18-2.25 (m, 1H), 2.27 (br, 1H), 3.80 (s, 3H), 3.90 (brq, 1H, *J*=6.5Hz), 4.51-4.59 (m, 1H), 6.04 (dd, 1H, *J*=7.5, 16.0Hz), 6.54 (d, 1H, *J*=16.0Hz), 6.84 (d, 2H, *J*=9.0Hz), 7.32 (d, 1H, *J*=9.0Hz). ^{13}C-NMR ($CDCl_3$) δ: 8.11 (q), 17.26 (q), 29.47 (t), 30.18 (t), 33.65 (t), 55.27 (q), 70.62 (d), 82.23 (d), 88.94 (s), 113.93 (d), 127.71 (d), 128.46 (d), 129.54 (s), 130.68 (d), 159.26 (s). EI-MS *m/z* (%): 276 (M^+, 21), 231 (48), 213 (33), 159 (58), 134 (36), 121 (63), 57 (100). HR-MS *m/z* Calcd for $C_{17}H_{24}O_3$ (M^+): 276.17251. Found: 276.17152.

Acid-Catalized Cyclization of 19

CSA (0.3mg, 1.29μmol) was added to a stirred solution of **19** (20mg, 68μmol) in CH_2Cl_2 (1ml) at room temperature. After 10 min, the reaction mixture was neutralized with Et_3N (0.05ml), and evaporated *in vacuo* to leave an oil, which was chromatographed on a preparative silica gel plate (*n*-hexane-ether 3:2) to give **27** (5.0mg, 27%) and **28** (7.5mg, 40%) as colorless oils.

(1*S*,2*RS*,4*R*,5*S*)-5-Ethyl-4-methyl-3,8-dioxabicyclo[3.2.1]octan-2-ol (29)

NMO (516mg, 3.82mmol) and OsO_4 (9.0mg) were added to a stirred solution of **28** (0.7g, 2.54mmol) in acetone (6.5ml) and H_2O (1.3ml) at room temperature. After 6 hr, $Na_2S_2O_4$ (0.2g), powdered 3A molecular sieves (0.9g), and H_2O (6ml) were added, and stirring was continued for 8 hr. The insoluble materials were

filtered off, and the filtrate was adjusted to pH 7 with 2% H_2SO_4, and concentrated *in vacuo*. After adjustment to pH 1, the mixture was extracted with ether. The extract was dried with Na_2SO_4 in the presence of $NaHCO_3$, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (CH_2Cl_2-MeOH 50:1) to give (2*S*,5*S*)-2-ethyl-2-[(1*R*)-1-hydroxyethyl]-5-[(1*RS*,2*RS*)-1,2-dihydroxy-2-(4-methoxyphenyl)ethyl]tetrahydrofuran as a colorless oil (0.64g, 81%). EI-MS *m/z* (%): 310 (M^+, 0.1): 292 (M^+-18, 0.2), 265 (1.3), 247 (8.6), 175 (3.3), 156 (22), 137 (100), 115 (37).

$NaIO_4$ (221mg) was added to a stirred solution of the above triol (158mg, 0.51mmol) in 50% MeOH (4ml) at 0°C. After 1 hr, the reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to remove MeOH. The aqueous layer was saturated with NaCl, and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 5:1-1:1) to give (2*S*,5*S*)-2-ethyl-5-formyl-2-[(1*R*)-1-hydroxyethyl]tetrahydrofuran as a colorless oil (83.5mg, 96%). IR (neat) ν (cm^{-1}): 3550, 1720. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (t, 3H, *J*=7.5Hz), 1.12 (d, 3H, *J*=6.5Hz), 1.56 (q, 2H, *J*=7.5Hz), 1.53-1.78 (m, 2H), 1.85-1.99 (m, 1H), 2.03-2.35 (m, 2H), 3.96 (q, 1H, *J*=6.5Hz), 4.26-4.44 (m, 1H), 9.67 (d, 1H, *J*=2.0Hz). EI-MS *m/z* (%): 155 (M^+-17, 3.0), 143 (28), 127 (100), 97 (56).

Powdered KOH (40mg) was added to a stirred solution of the above aldehyde (48.5mg, 282μmol) in MeOH (2.5ml). After 2 hr at 40°C, $NaHCO_3$ (100mg) was added, and the mixture was concentrated *in vacuo*. The residue was passed through a short silica gel column (CH_2Cl_2-MeOH 20:1), and the eluate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 3:1) to give **29** as a colorless oil (35.2mg, 72.5%). IR (neat) ν (cm^{-1}): 3500. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (t, 3H, *J*=7.5Hz), 1.04 (d, 12/5H, *J*=6.5Hz), 1.07 (d, 3/5H, *J*=7.0Hz), 1.40-1.71 (m, 3H), 1.86-2.11 (m, 3H), 2.81 (d, 1/5H, *J*=6.5Hz), 3.68 (d, 4/5H, *J*=10.5Hz), 3.89 (q, 1/5H, *J*=7.0Hz), 4.07 (q, 4/5H, *J*=6.5Hz), 4.12 (d, 1H, *J*=6.5Hz), 4.62 (d, 4/5H, *J*=10.0Hz), 4.95 (d, 1/5H, *J*=4.5Hz). EI-MS *m/z* (%): 173 (M^++1, 1.2), 172 (M^+, 10), 155 (7.2), 154 (5.2), 143 (3.6), 128 (6.9), 127 (13), 126 (11), 109 (3.7), 100 (34), 99 (39), 98 (31), 81 (26), 72 (96), 57 (100). HR-MS *m/z* Calcd for $C_9H_{16}O_3$ (M^+): 172.11004. Found: 172.10954.

(2*S*,5*R*)-2-[(1*R*)-1-Benzyloxymethoxyethyl]-5-*tert*-butyldimethylsilyloxymethyl-2-ethyltetrahydrofuran (30)

$LiAlH_4$ (110mg, 2.9mmol) was added to a stirred solution of **29** (220mg, 1.28mmol) in ether (10ml) at 0°C. After 5 min, a mixture of ether and MeOH (10:1) was carefully added, and then H_2O (0.1ml), 15% NaOH (0.1ml), H_2O (0.3ml), and $MgSO_4$ were successively added. After being stirred for 3 hr, the mixture was filtered, and washed with ether. The filtrate was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (CH_2Cl_2-MeOH 80:1) to give (2*S*,5*R*)-2-ethyl-2-[(1*R*)-1-hydroxyethyl]-5-hydroxymethyltetrahydrofuran as a colorless oil (224mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (t, 3H, *J*=7.0Hz), 1.11 (d, 3H, *J*=6.0Hz), 1.30-1.66 (m, 3H), 1.81-2.28 (m, 3H), 2.41-3.20 (br, 2H), 3.54 (dd, 1H, *J*=4.0, 11.0Hz), 3.85 (dd, 1H, *J*=3.0, 11.0Hz), 3.88 (q, 1H, *J*=6.0Hz), 4.13 (dddd, 1H, *J*=3.0, 4.0, 6.0, 7.0Hz). EI-MS *m/z* (%): 145 (M^+-29, 4.0), 143 (19), 129 (100).

Imidazole (127mg, 1.87mmol) and then a solution of TBS chloride (146.5mg, 973μmol) in CH_2Cl_2 (0.4ml) were added to a stirred solution of the above diol (130mg, 747μmol) at 0°C. After being stirred at room temperature overnight, H_2O was added, and stirring was continued for 4 hr. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4 and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 10:1) to give (2*S*,5*R*)-5-*tert*-butyldimethylsilyloxymethyl-2-ethyl-2-[(1*R*)-1-hydroxyethyl]tetrahydrofuran as a

colorless oil (200mg, 93%). IR (neat) ν (cm^{-1}): 3400. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (s, 6H), 0.91 (s, 9H), 0.92 (t, 3H, *J*=7.0Hz), 1.08 (d, 3H, *J*=6.5Hz), 1.47 (q, 2H, *J*=7.0Hz), 1.60-2.19 (m, 4H), 3.19 (br, 1H), 3.56 (dd, 1H, *J*=2.0, 8.5Hz), 3.82 (q, 1H, *J*=6.5Hz), 3.94 (dd, 1H, *J*=3.0, 8.5Hz), 3.92-4.18 (m, 1H). EI-MS *m/z* (%): 259 (M^+ -29, 1.3), 243 (34), 171 (44), 75 (100). HR-MS *m/z* Calcd for $C_{13}H_{27}O_3Si$ (M^+-29): 259.17291. Found: 259.17188.

(*i*-Pr)$_2$EtN (0.7ml), benzyloxymethyl (BOM) chloride (0.5ml), and 4-*N*,*N*-dimethylaminopyridine (DMAP) (8mg) were successively added to a stirred solution of the above alcohol (316mg, 1.1mmol) in CH_2Cl_2 (6ml). After being stirred at room temperature overnight, H_2O was added, stirring was continued for 3 hr, and then CH_2Cl_2 and 2N HCl were added. The CH_2Cl_2 layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 25:1) to give **30** as a colorless oil (387mg, 86%). $[\alpha]_D^{10}$ +18° (c=6.37, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.04 (s, 6H), 0.88 (s, 9H), 0.91 (t, 3H, *J*=7.0Hz), 1.17 (d, 3H, *J*=6.5Hz), 1.57 (q, 2H, *J*=7.0Hz), 1.58-2.00 (m, 4H), 3.51 (dd, 1H, *J*=6.5, 10.0Hz), 3.69 (dd, 1H, *J*=4.0, 6.0Hz), 3.73 (q, 1H, *J*=6.5Hz), 4.62 (s, 2H), 4.81 (s, 2H), 7.33 (s, 5H). EI-MS *m/z* (%): 379 (M^+-29, 0.2), 321 (2.5), 243 (47), 171 (24), 91 (100). HR-MS *m/z* Calcd for $C_{21}H_{35}O_4Si$ (M^+-29): 379.23306. Found: 379.23041.

(2*S*,5*R*)-2-Ethyl-2-[(1*R*)-1-hydroxyethyl]-5-[(1*E*)-2-(4-methoxyphenyl)ethenyl]tetrahydrofuran (27)

A solution of **28** (573mg, 2.06mmol) in CH_2Cl_2 (5ml) was treated with Ac_2O (0.3ml), Et_3N (0.5ml) and DMAP (2mg) as usual to give the acetate as a colorless oil (660mg). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (t, 3H, *J*=7.0Hz), 1.23 (d, 3H, *J*=6.5Hz), 2.07 (s, 3H), 3.80 (s, 3H). 4.98 (q, 1H, *J*=6.5Hz), 6.03 (dd, 1H, *J*=7.0, 16.0Hz).

A solution of the above acetate (660mg) and CSA (28.6mg) in CH_2Cl_2 (6ml) was stirred at room temperature for 24 hr. After addition of Et_3N, the mixture was evaporated *in vacuo*. The residue was passed through a silica gel column (*n*-hexane-EtOAc) to give a colorless oil (660mg), which was dissolved in ether (6ml) and treated with $LiAlH_4$ (74mg). After 5 min, usual work-up and chromatography on a silica gel column (*n*-hexane-EtOAc 10:1) gave the recovered **28** (339mg, 59%) and **27** as a colorless oil (232mg, 41%). $[\alpha]_D^{15}$ +33° (c=1.03, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.96 (t, 3H, *J*=7.5Hz), 1.14 (d, 3H, *J*=6.5Hz), 1.51 (dq, 1H, *J*=14.0, 7.5Hz), 1.64 (dq, 1H, *J*=14.0, 7.5Hz), 1.53-1.63 (m, 1H), 1.70-1.81 (m, 1H), 2.08-2.20 (m, 2H), 2.29 (br, 1H), 3.80 (s, 3H), 3.86 (q, 1H, *J*=6.5Hz), 4.50-4.57 (m, 1H), 6.07 (dd, 1H, *J*=7.5, 16.0Hz), 6.55 (d, 1H, *J*=16.0Hz), 6.84 (d, 2H, *J*=8.5Hz), 7.32 (d, 2H, *J*=9.0Hz). ^{13}C-NMR ($CDCl_3$) δ: 8.08 (q), 17.22 (q), 29.44 (t), 29.59 (t), 33.46 (t), 55.29 (q), 69.87 (d), 80.08 (d), 89.13 (s), 113.98 (d), 127.66 (d), 127.76 (d), 129.41 (s), 131.08 (d), 159.35 (s), EI-MS *m/z* (%): 276 (M^+, 22), 231 (58), 214 (6.5), 213 (35), 173 (11), 161 (17), 160 (32), 159 (60), 147 (12), 134 (37), 121 (66), 57 (100). HR-MS *m/z* Calcd for $C_{17}H_{24}O_3$ (M^+): 276.17251. Found: 276.17154.

(2*S*,5*R*)-2-[(1*R*)-1-Benzyloxymethoxyethyl]-2-ethyl-5-formyltetrahydrofuran (11)

a) 1N HCl (2ml) was added to a stirred solution of **30** (387mg, 949μmol) in THF (10ml) at room temperature. After 2 hr, the reaction mixture was neutralized with $NaHCO_3$, and extracted with ether. The extract was dried over Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 5:1) to give (2*S*,5*R*)-2-[(1*R*)-1-benzyloxymethoxyethyl]-2-ethyl-5-hydroxymethyltetrahydrofuran as a colorless oil (271 mg, 97%). $[\alpha]_D^{13}$ -21° (c=5.10, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (t, 3H, *J*=7.0Hz), 1.17 (d, 3H, *J*=6.5Hz), 1.42-1.70 (m, 3H), 3.78 (dd, 1H, *J*=2.0, 9.0Hz),

3.91 (q, 1H, *J*=6.5Hz), 4.65 (s, 2H), 4.85 (s, 2H), 7.34 (s, 5H). ^{13}C-NMR ($CDCl_3$) δ: 7.62 (q), 15.94 (q), 27.72 (t), 29.72 (t), 30.18 (t), 65.90 (t), 69.44 (t), 69.44 (t), 76.64 (d), 79.87 (d), 88.39 (s), 93.66 (t), 127.51 (d), 127.74 (d), 128.35 (d), 137.68 (s).

A solution of DMSO (0.27ml) in CH_2Cl_2 (0.8ml) was added to a stirred solution of oxalyl chloride (0.16ml, 1.84mmol) in CH_2Cl_2 (4ml) at -78°C under argon. After 2 min, a solution of the above alcohol (108mg, 367μmol) in CH_2Cl_2 (1.2ml) was added, stirring was continued for 30 min, and then Et_3N (1.1ml, 1.84mmol) was added. After 3 hr, CH_2Cl_2 and H_2O were added, the aqueous layer extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 3:1) to give **11** as a colorless oil (100mg, 93%). $[\alpha]_D^{20}$ -49° (c=3.43, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (t, 3H, *J*=7.0Hz), 1.20 (d, 3H, *J*=6.0Hz), 1.50-1.75 (m, 3H), 2.02 -2.17 (m, 3H), 3.83 (q, 1H, *J*=6.5Hz), 4.28 (ddd, 1H, *J*=1.5, 7.0, 7.5Hz), 4.58 (d, 1H, *J*=11.5Hz), 4.66 (d, 1H, *J*=11.5Hz), 4.81 (d, 1H, *J*=6.5Hz), 4.85 (d, 1H, *J*=6.0Hz), 7.26-7.37 (m, 5H), 9.67 (d, 1H, *J*=1.5Hz). EI-MS *m/z* (%): 263 (M^+-29, 0.3), 233 (0.5), 186 (1.0), 155 (2.7), 127 (58), 91 (100). HR-MS *m/z* Calcd for $C_{16}H_{23}O_3$ (M^+-29): 263.16469. Found: 263.16367.

b) A solution of **27** (215mg, 0.77mol) in CH_2Cl_2 (2ml) was treated with BOM chloride (0.5ml) in the presence of (*i*-Pr)$_2$EtN (1ml) at room temperature. Work-up as described for **22** gave the BOM ether as a colorless oil (309mg, 100%). $[\alpha]_D^{18}$ +24° (c=0.392, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.96 (t, 3H, *J*=7.5Hz), 1.22 (d, 3H, *J*=6.5Hz), 1.51-2.13 (m, 4H), 3.80 (s, 3H), 4.09 (q, 1H, *J*=6.5Hz), 4.46-4.70 (m, 1H). 4.66 (s, 2H), 4.87 (s, 2H), 6.04 (dd, 1H, *J*=7.0, 16.0Hz), 6.52 (d, 1H, *J*=16.0Hz), 6.82 (d, 2H, *J*=9.5Hz), 7.28 (d, 2H, *J*=9.5Hz), 7.33 (s, 5H). FAB-MS *m/z* (%): 397 (MH^+, 43), 395 (20), 391 (26), 353 (7.7), 307 (14), 289 (25), 275 (41), 259 (11), 244 (44), 231 (62), 173 (43), 154 (57), 147 (51), 136 (37), 121 (51), 91 (100). HR-MS *m/z* Calcd for $C_{25}H_{33}O_4$ (MH^+): 397.2378. Found: 397.2357.

The BOM ether (491mg, 1.23mmol) was oxidized with NMO (202mg) and OsO_4 (10mg) as described for **21** to give the diol as a colorless oil (435mg, 82%). IR (neat) ν (cm^{-1}): 3440. FAB-MS *m/z* (%): 431 (MH^+, 3.4), 429 (3.4), 413 (15), 391 (27), 321 (8.9), 307 (20), 305 (42), 289 (13), 275 (18), 263 (74), 247 (11), 233 (8.9), 219 (7.2), 185 (7.4), 163 (20), 154 (80), 149 (31), 137 (100), 121 (22), 91 (100). HR-MS Calcd for $C_{25}H_{35}O_6$ (MH^+): 431.2425. Found: 431.2446.

The diol (384mg, 0.89mmol) was cleaved with $NaIO_4$ (250mg) to give **11** as a colorless oil (222.5mg, 85%).

(2*S*,3*R*,6*R*)-3-Benzyloxy-3-ethyl-6-[(1*E*)-2-(4-methoxyphenyl)ethenyl]-2-methyltetrahydropyran (31)

$ZnBr_2$ (59mg, 0.26mmol) was added to a stirred solution of **25** (94mg, 0.243mmol) in CH_2Cl_2 (3ml) at -20°C under argon. After 1.5 hr, Et_3N (0.1ml) was added, and the mixture was passed through a short silica gel column. The eluate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 15:1) to give colorless oils of **31** (66.1mg, 74%) and the 6*S* isomer (**32**) (4.9mg, 5.4%). **31**: $[\alpha]_D^{18}$ +5.3° (c=0.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (t, 3H, *J*=7.5Hz), 1.31 (d, 3H, *J*=6.5Hz), 1.37-1.71 (m, 5H), 1.80-1.99 (m, 2H), 3.94 (s, 3H), 4.16 (q, 1H, *J*=6.5Hz), 4.27-4.33 (m, 1H), 4.36 (d, 1H, *J*=11.5Hz), 4.50 (d, 1H, *J*=11.5Hz), 6.12 (dd, 1H, *J*=6.0, 16.0Hz), 6.54 (d, 1H, *J*=16.0Hz), 6.84 (d, 2H, *J*=9.0Hz), 7.22-7.36 (m, 3H), 7.32 (d, 2H, *J*=9.0Hz), 7.41-7.44 (m, 2H). FAB-MS *m/z* (%): 367 (MH^+, 37), 341 (5.3), 307 (39), 289 (21), 275 (21), 260 (38), 231 (18), 173 (40), 154 (100), 136 (66), 121 (40), 107 (22), 91 (67). HR-MS *m/z* Calcd for $C_{24}H_{31}O_3$ (MH^+): 367.2272. Found: 367.2294. **32**: ^{1}H-NMR ($CDCl_3$)

δ: 0.99 (t, 3H, *J*=7.5Hz), 1.24 (d, 3H, *J*=6.5Hz), 1.55-1.90 (m, 6H), 2.09-2.14 (m, 1H), 3.78 (q, 1H, *J*=6.5Hz), 3.80 (s, 3H), 4.03-4.10 (m, 1H), 4.50 (d, 1H, *J*=11.5Hz), 4.59 (d, 1H, *J*=11.5Hz), 6.09 (dd, 1H, *J*=6.0, 16.0Hz), 6.54 (d, 1H, *J*=16.0Hz), 6.84 (d, 2H, *J*=9.0Hz), 7.32 (d, 2H, *J*=9.0Hz), 7.25-7.36 (m, 5H).

(2*S*,3*R*,6*R*)-3-Benzyloxy-3-ethyl-6-formyl-2-methyltetrahydropyran (12)

31 (657mg, 1.63mmol) was oxidized with OsO_4 (15mg) in the presence of NMO (500mg, 3.7mmol) in acetone (10ml) and H_2O (1.0ml) at room temperature overnight. $Na_2S_2O_4$ (0.2g), powered 3A molecular sieves (0.9g) and H_2O (3.0ml) were added into the resultant and then the aqueous mixture was vigorously stirred for 2.0 hr at room temperature. After removal of the insoluble solid by suction filtration, the filtrate was extracted with ether (50ml x 3). The extract was washed with 0.1N HCl, H_2O and brine, then dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 8 : 1) to give the diol as a colorless oil (718mg, 100%). IR (neat) ν (cm^{-1}): 3450, 1620. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (t, 3H, *J*=7.0Hz), 1.21 (d, 3Hx1/4, *J*=7.0Hz), 1.23 (d, 3Hx3/4, *J*=7.0Hz), 3.80 (s, 3Hx3/4), 3.81 (s, 3Hx1/4), 4.14 (brd, 1H, *J*=7.0Hz), 4.65 (d, 1Hx1/4, *J*=6.5Hz), 4.90 (d, 1Hx3/4, *J*=3.5Hz), 6.97 (d, 2H, *J*=9.0Hz). FAB-MS *m/z* (%): 399 (M^+-1, 6.2), 383 (22), 365 (22), 341 (3.1), 307 (12), 291 (9.4), 289 (9.5), 275 (100), 263 (12), 234 (27), 233 (99), 219 (17), 154 (61), 137 (98), 121 (47), 91 (99). HR-MS Calcd for $C_{24}H_{31}O_5$ (M^+-1): 399.2164. Found: 399.2188.

The diol (804mg, 2.0mmol) was cleaved with $NaIO_4$ (860mg, 4.0mmol) to give **12** as a colorless oil (430mg, 82%). $[\alpha]_D^{18}$ +11° (c=0.4, $CHCl_3$). IR (neat) ν (cm^{-1}): 1745, 1610. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (t, 3H, *J*=7.5Hz), 1.29 (d, 3H, *J*=7.0Hz), 1.52 (dt, 1H, *J*=15.0, 7.5Hz), 1.61 (dt, 1H, *J*=15.0, 7.5Hz), 1.66-1.74 (m, 2H), 1.84-1.98 (m, 2H), 4.05 (dd, 1H, *J*=4.0, 9.5Hz), 4.13 (q, 1H, *J*=7.0Hz), 4.34 (d, 1H, *J*=11.0Hz), 4.46 (d, 1H, *J*=11.0Hz), 7.31-7.37 (m, 5H), 9.71 (s, 1H). FAB-MS *m/z* (%): 263 (MH^+, 12), 219 (21), 154 (100), 138 (47), 137 (92), 136 (99), 107 (24), 91 (52). HR-MS *m/z* Calcd for $C_{16}H_{23}O_3$ (MH^+): 263.1625. Found: 263.1625.

References and Notes

1. Chiral synthesis of polyketide derived natural products. 41. For part 40, see: K. Horita, K.Tanaka, T. Inoue, and O. Yonemitsu, *Tetrahedron Lett.*, **33**, 5541 (1992).
2. a) T. L. B. Boivin, Tetrahedron, **43**, 3309 (1987); b) G. Cardillo and M. Orena, *Ibid.*, **46**, 321 (1990).
3. Total synthesis of polyether antibiotics. Calcimycin: a) D. A. Evans, C. E. Sacks, W. A. leschick, and T. R. Taber, *J. Am. Chem. Soc.*, **101**, 6789 (1979); b) G. R. Martinez, P. A. Grieco, E. Williams, K. Kanai, and C. V. Srinivasan, *Ibid.*, **104**, 1436 (1982); c) Y. Nakahara, A. Fujita, K. Beppu, and T. Ogawa, *Tetrahedron*, **42**, 6465 (1986); d) D. P. Negri and Y. Kishi, *Tetrahedron Lett.*, **28**, 1063 (1987). Monensin: e) T. Fukuyama, K. Akasaka, D. S. Karanewsky, C.-L. J. Wang, G. Schmid, and Y. Kishi, *J. Am. Chem. Soc.*, **101**, 262 (1979); f) W. C. Still, J. McDonald, and D. Collum, *Ibid.*, **102**, 2117 (1980). Lasalocid A: g) T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, *Ibid.*, **100**, 2933 (1978); h) R. E. Ireland, S. Thaisrivongs, and C. S. Wilcox, *Ibid.*, **102**, 1155 (1980); i) R. E. Ireland, R. C. Anderson, A. R. Bodoud, B. J. Fitzsimmons, G. J. McGarrey, S. Thaisrivongs, and S. C. Wilcox, *Ibid.*, **105**, 1988 (1983); J) I. Noda, K. Horita, Y. Oikawa, and O. Yonemitsu, *Tetrahedron Lett.*, **31**, 6035 (1990). Narasin: k) Y. Kishi, *Aldrichim. Acta*,

13, 23 (1980). Salinomycin: 1) Y. Kishi, S. Hatakeyama, and M. D. Lewis, "Front. Chem. Plenary Keynote Lect. IUPAC Congr. 28th, 1981," ed by K. J. Laidler, Pergamon Press, Oxford, 1982, pp 287-304; m) K. Horita, Y. Oikawa, S. Nagato, and O. Yonemitsu, *Chem. Pharm. Bull.*, **37**, 1717 (1989). X-206: n) D. A. Evans, S. L. Bender, and J. Morris, *J. Am. Chem. Soc.*, **110**, 2506 (1988). Ionomysin: o) D. A. Evans, R. L. Dow, T. L. Shin, J. M. Takacs, and R. Zahler, *Ibid.*, **112**, 5290 (1990). Ferensimysin B: p) D. A. Evans, R. P. Polmaszek, K. M. DeVries, D. E. Guinn, and D. J. Mathre, *Ibid.*, **113**, 7613 (1991). Lysocellin: q) K. Horita, K. Tanaka, T. Inoue, and O. Yonemitsu, *Tetrahedron Lett.*, **33**, 5541 (1992).

4. I. Noda, K. Horita, Y. Oikawa, and O. Yonemitsu, *Tetrahedron Lett.*, **27**, 1917 (1986). *cf.* Y. Oikawa, K. Horita, and O. Yonemitsu, *Heterocycles*, **23**, 553 (1985).
5. J. W. Westley, J. F. Blount, R. H. Evans, Jr., A. Stempel, and J. Berger, *J. Antibiot.*, **27**, 597
6. J. Berger, A. Rachlin, W. E. Scott, L. H. Sternback, and M. W. Glodberg, *J. Am. Chem. Soc.*, **73**, 5925 (1951).
7. Unless otherwise noted, numbering is based on those of isolasalocid A (**9**) and lasalocid A (**10**).
8. a) T. Shono, Y. Matsumura, H. Hamaguchi, and S. Naitoh, *J. Org. Chem.*, **48**, 5126 (1983); b) . M. J. Tronchet, R. Graf, and R. Gurny, *Helv. Chim. Acta*, **55**, 613 (1972).
9. L. Banfi, A. Bernardi, L. Colombo, C. Gennari, and C. Scolastico, *J. Org. Chem.*, **49**, 3784 (1984).
10. a) A. J. Mancuso, S. L. Hung, and D. Swern, *J. Org. Chem.*, **43**, 2480 (1978); b) A. J. Mancuso and D. Swern, *Synthesis*, 165 (1981).
11. a) W. C. Still and J. H. McDonald III, *Tetrahedron Lett.*, 1031 (1980); b) W. C. Still and J. A. Schneider, *Ibid.*, 1035 (1980).