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Highly Stereocontrolled Total Synthesis of the Polyether Antibiotic Salinomycin. I. Synthesis of the Left (C1—C9) and Middle (C10—C17) Segments from D-Glucose[1]

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The required left (C1—C9) segment, (*R*)-2-[(2*R*,5*S*,6*R*)-6-[(*R*)-1-formylethyl]-5-methyltetrahydropyran-2-yl]butanoic acid, for a total synthesis of salinomycin was highly stereoselectively synthesized from D-glucose *via* a chelation-controlled Grignard reaction and a decarbonylation with Wilkinson's catalyst as important steps. The stereoselective synthesis of the middle (C10—C17) segment, (2*R*,4*S*,5*S*,6*R*)-6-ethyl-2,4-dimethyl-7-oxononan-5-olide, starting from D-glucose is also described.

Keywords polyether antibiotic; salinomycin; stereoselective synthesis; 4-methoxybenzyl-protection; Wittig–Horner coupling; chelation-controlled Grignard reaction; tetrahydropyran ring formation; decarbonylation

Many modern synthetic methodologies have been established through formidable and ingeniously devised total syntheses of complex natural products such as polyketide derived macrolide and polyether antibiotics. We also planned to synthesize highly stereoselectively a series of representative antibiotics by virtue of a common methodology starting from D-glucose as a chiral starting material. Recent developments in macrolide synthesis include the use of some stereoselective reactions and benzyl-type protecting groups to synthesize several typical aglycones such as 12-membered-ring methynolide,[2] 14-membered-ring pikronolide[3] and erythronolide A,[1,4] and 16-membered-ring tylonolide.[5] As the first application of our synthetic methodology to the polyether series, we decided to synthesize salinomycin (**1**), a representative polyether antibiotic.

Salinomycin (**1**), isolated from *Streptomyces albus* by Miyazaki *et al.* in 1974,[6] is now widely used as an anticoccidal agent in the poultry industry. Because of its complex chemical structure and potent biological activity, **1** has attracted synthetic attention, and the first total synthesis was announced by Kishi *et al.*[7] Connection of three segments, **2**, **3**, and **4**, was the basis of our synthetic plan, in which the stereoselectivity for the construction of each of the new chiral centers would be at least 10 : 1. We report here a highly stereocontrolled synthesis of **1**,[8] describing the synthesis of the left (**2**) and middle segments (**3**) in this paper, the synthesis of the right segment (**4**) in the second paper,[9] the synthesis of Kishi's intermediate (**5**)[7] and the total synthesis in the third,[10] and selective cleavage of **1** in the fourth.[11]

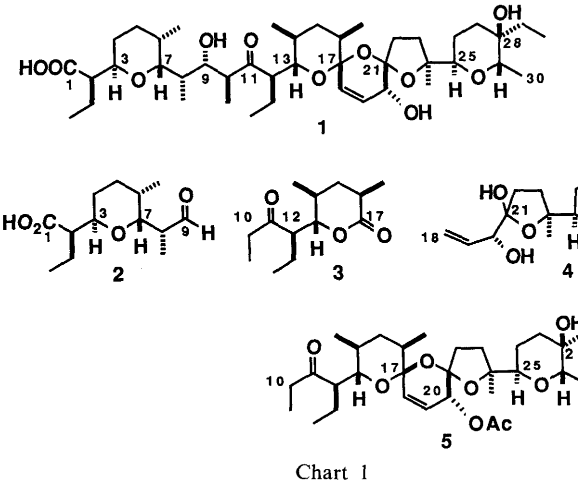
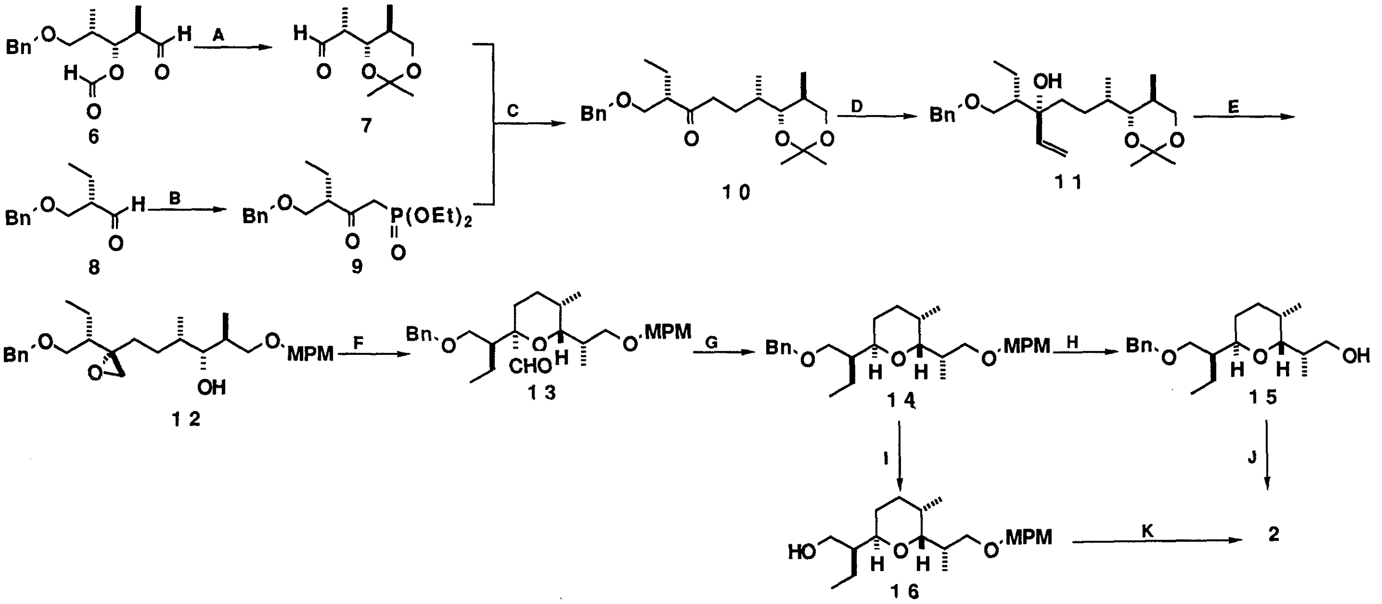


Chart 1

Synthesis of the Left Segment (2) Since the left (C1—C9) segment (**2**) has a thermodynamically unfavorable 2,6(C3,C7)-*trans*-substituted tetrahydropyran ring, it should be constructed by a kinetic method, not by a thermodynamical method.[12]

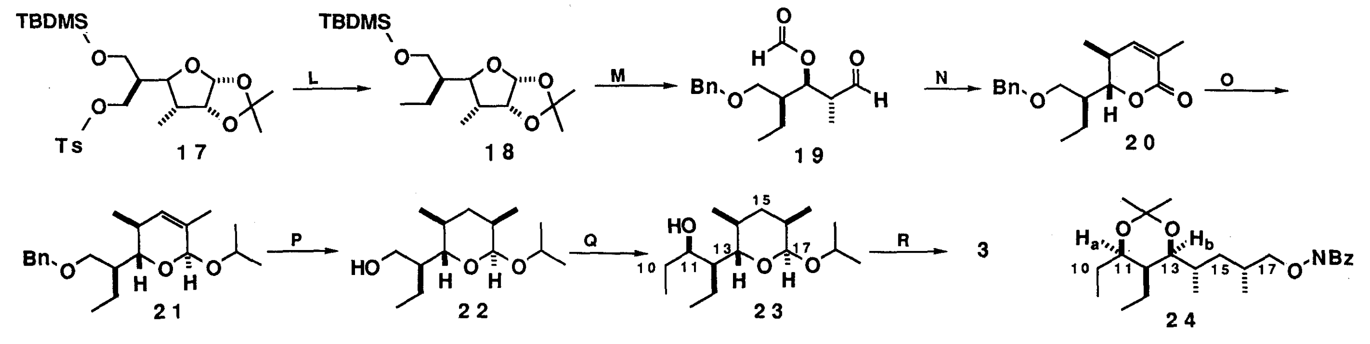
The aldehyde (**6**),[2a,b] an intermediate from D-glucose to methynolide, was readily converted to **7** in excellent yield *via* four conventional reactions, lithium aluminum hydride reduction, isopropylidene protection, catalytic hydrogenolysis, and Swern oxidation. The other aldehyde (**8**)[13] was treated with the lithium salt of diethyl methanephosphonate, and then Swern oxidation gave the ketophosphonate (**9**), which was condensed with **7**. The Wittig–Horner reaction proceeded quite smoothly at room temperature, and the resulting (*E*)-α,β-enone was reduced to the ketone (**10**) in quantitative yield. When **10** was treated with vinylmagnesium bromide at −78 °C, the expected alcohol (**11**) was obtained with 13 : 1 selectivity *via* the chelation-controlled Grignard reaction with a six-membered cyclic transition state, although such a high stereoselectivity usually would not be expected.[14] In the sequence of five conventional reactions **11** was converted to the epoxide (**12**)[15] in which the two primary hydroxy groups were protected with benzyl (Bn) and 4-methoxybenzyl (MPM) groups in excellent yield, and then readily recyclized to the tetrahydropyran (**13**) by treatment with camphorsulfonic acid (CSA) followed by Swern oxidation. Since decarbonylation with Wilkinson's catalyst is known to proceed with retention of configuration,[16] **13** was treated with the catalyst. However, on heating in the usual solvent (benzonitrile) at 160 °C, only a small amount of the expected 2,6-*trans*-tetrahydropyran (**14**) was obtained, because the carbonyl group of **13** is in a sterically crowded position. Acceptable amounts of **14** were obtained when an acetonitrile solution was heated in a sealed tube.[17]

Conversion of **14** into the left segment (**2**) was performed *via* two pathways using selective deprotection of either Bn or MPM. When **14** was first treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), the selective deprotection of the MPM group[15] proceeded quantitatively to give **15**, which was then converted to **2** in 53% overall yield *via* five conventional reactions, Swern oxidation, acetalization, catalytic hydrogenation to remove the Bn protection, Jones oxidation, and final removal of the acetal protection.



(A) 1) LiAlH$_4$, THF; 2) Me$_2$C(OMe)$_2$, CSA, MeCOMe; 3) Pd–C, H$_2$, EtOH; 4) DMSO, (COCl)$_2$, CH$_2$Cl$_2$, Et$_3$N (B) 1) MePO(OEt)$_2$, *n*-BuLi, Et$_2$O–hexane; 2) DMSO, (COCl)$_2$, CH$_2$Cl$_2$, Et$_3$N (C) 1) NaH, DMF–THF; 2) Pd–C, H$_2$ (D) CH$_2$=CHMgBr, THF, −78 °C (E) 1) O$_3$, CH$_2$Cl$_2$, −78 °C, NaBH$_4$, MeOH; 2) MsCl, Et$_3$N, toluene, 0 °C; 3) 1 N HCl, THF; 4) K$_2$CO$_3$, MeOH–H$_2$O; 5) MPMCl, NaH, DMSO (F) 1) CSA, CH$_2$Cl$_2$; 2) DMSO, (COCl)$_2$, CH$_2$Cl$_2$, Et$_3$N (G) (Ph$_3$P)$_3$RhCl, MeCN, 160 °C (H) DDQ, CH$_2$Cl$_2$–H$_2$O (I) Raney Ni, H$_2$, EtOH (J) 1) DMSO, (COCl)$_2$, CH$_2$Cl$_2$, Et$_3$N; 2) (CH$_2$OH)$_2$, TsOH, C$_6$H$_6$, reflux; 3) Pd–C, H$_2$, EtOAc; 4) CrO$_3$, H$_2$SO$_4$, MeCOMe, 0 °C; 5) 2 N HCl, THF (K) 1) CrO$_3$, H$_2$SO$_4$, MeCOMe, 0 °C; 2) Pd–C, H$_2$, EtOAc; 3) PCC, MS, CH$_2$Cl$_2$

Chart 2



NBz = 4-NO$_2$-C$_6$H$_4$CO

(L) MeLi, CuI, Et$_2$O (M) 1) 1 N HCl, MeOH; 2) BnCl, NaH, DMSO–THF; 3) 4 N HCl, THF, 45 °C; 4) NaIO$_4$, THF–MeOH (N) 1) MeO$_2$CCHMePO(OMe)$_2$, NaH, THF; 2) K$_2$CO$_3$, MeOH (O) 1) DIBAH, toluene, −80 °C; 2) CSA, iso-PrOH (P) 1) Raney Ni, H$_2$, EtOH; 2) Rh–Al$_2$O$_3$, H$_2$, Et$_2$O (Q) 1) DMSO, (COCl)$_2$, CH$_2$Cl$_2$, Et$_3$N; 2) EtMgBr, Et$_2$O (R) 1) 4 N HCl, THF, 45 °C; 2) PCC, MS, CH$_2$Cl$_2$

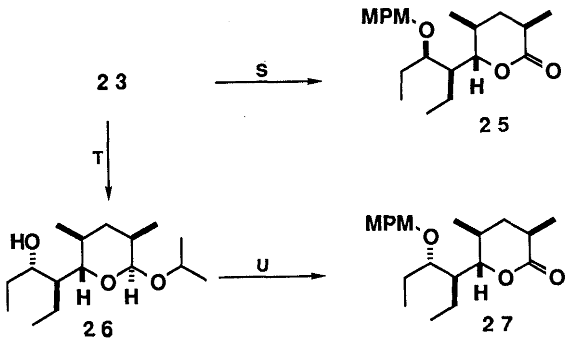
Chart 3

Alternatively, when **14** was first hydrogenated over Raney nickel, completely selective deprotection of the Bn group[15b,19] proceeded to give **16**, which was also readily converted to **2** *via* only three consecutive reactions, Jones oxidation, catalytic hydrogenation with palladium on charcoal (Pd–C), and pyridinium chlorochromate (PCC) oxidation.

Synthesis of the Middle Segment (3) For the synthesis of the middle (C10—C17) segment (**3**), the methodology developed in the course of the total synthesis of macrolide aglycones[2−5] was directly applied. Compound **17**[2a,b] was first treated with lithium dimethylcuprate to give **18** quantitatively, and this was readily converted to **19**, a homolog of **6**, in 78% overall yield. Wittig–Horner reaction of **19** using trimethyl 2-phosphonopropionate[20] followed by treatment with potassium carbonate gave the α,β-unsaturated lactone (**20**).[21] Diisobutylaluminum hydride (DIBAH) reduction and CSA treatment in isopropanol gave **21** as the sole anomer, which was hydrogenated with Raney nickel and subsequently with rhodium on alumina to give **22** with 13 : 1 stereoselectivity.[22]

Swern oxidation of **22** followed by Grignard reaction with ethylmagnesium bromide at −50 °C gave only the Cram adduct (**23**) in excellent yield. The configuration of **23** was confirmed after conversion to **24**, in which an 8% nuclear Overhauser effect (NOE) was observed between H$_a$ and H$_b$. Conversion of **23** into **3** was readily and efficiently carried out by acid hydrolysis and PCC oxidation.

The highly stereoselective synthesis of the middle segment (**3**) was thus completed, but the C11 ketone (**3**) was not necessarily suitable as a synthetic intermediate. A C11 hydroxy compound **25** or **27** would be a more practically



(S) 1) MPMCl, NaH, DMF–THF; 2) 0.4 N HCl, THF, 55 °C; 3) PCC, MS, CH_2Cl_2 (T) 1) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N; 2) Red-al, toluene, −70—0 °C (U) 1) MPMCl, NaH; 2) 1 N HCl, THF, 50 °C; 3) PCC, MS, CH_2Cl_2

Chart 4

favorable intermediate.[23] The C11 hydroxy group of 23 was first protected with MPM,[15] then the isopropyl protection was removed by acid hydrolysis, and finally PCC oxidation of the resulting hemiacetal gave **25** in good yield. The synthesis of **27** from **23** was carried out as follows. The C11 hydroxy group of **23** was first oxidized (Swern oxidation) to the ketone, which was reduced with sodium bis(2-methoxyethoxy)aluminium hydride (Red-al) in toluene at −70 °C to give solely **26**,[24] stereoisomeric with **23**, in almost quantitative yield. Compound **26** was also readily converted to **27**.

Finally, it is worth noting that the stereoselectivities for the construction of the new chiral centers of the left (C1—C9) (**2**) and middle (C10—C15) segments (**3**) starting from D-glucose were quite high, namely 100, 93, 96, 97, 96, 97, and 98% for C2, C3, C6, C8, C12, C14, and C16 of **1**, respectively.

Experimental

Unless otherwise noted, physical data were measured as follows. Optical rotations were measured in $CHCl_3$ with a JASCO DIP-4 digital polarimeter. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded in $CDCl_3$ on a JEOL FX-200 (200 MHz) or JEOL JNM GX-270 (270 MHz) instrument. Mass spectra (MS) were taken on a JEOL JMS D-300 or JEOL JMS-01 SG spectrometer. Infrared (IR) spectra were recorded in $CHCl_3$ or neat on a JASCO IRA-2 spectrophotometer.

(2*R*,3*S*,4*S*)-3,5-Isopropylidenedioxy-2,4-dimethylpentanal (7) A solution of **6** (1.17 g, 4.43 mmol) in tetrahydrofuran (THF) (20 ml) was added dropwise to a stirred ice-cold suspension of $LiAlH_4$ (336 mg, 8.85 mmol) in THF (25 ml). After 30 min, the reaction was quenched with EtOAc, then work-up as usual gave the diol (1.1 g), which was dissolved in acetone (15 ml). This solution was stirred with 2,2-dimethoxypropane (3 ml) and CSA (30 mg) at room temperature for 30 min. The reaction mixture was neutralized with Et_3N and concentrated *in vacuo*. The residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 10) to afford (2*S*,3*R*,4*S*)-1-benzyloxy-3,5-isopropylidenedioxy-2,4-dimethylpentane as a colorless oil (1.2 g, 100%). $[\alpha]_D^{20}$ +41° (c=4.0). ^{1}H-NMR δ: 0.71 (3H, d, J=7 Hz), 0.87 (3H, d, J=7 Hz), 1.34 (3H, s), 1.39 (3H, s), 1.56—2.16 (2H, m), 3.21—3.78 (5H, m), 4.50 (2H, s), 7.33 (5H, s). MS m/z (relative intensity): 278 (M^+, 0.4), 263 (5.5), 220 (3.2), 91 (100). Exact MS m/z Calcd for $C_{17}H_{26}O_3$ (M^+): 278.1883. Found: 278.1869.

A solution of the above pentane (1.0 g) in EtOH (40 ml) was hydrogenated with 10% Pd–C (400 mg) at ordinary temperature and pressure for 3.5 h. After removal of the catalyst, evaporation of the solvent left (2*S*,3*R*,4*S*)-3,5-isopropylidenedioxy-2,4-dimethylpentanol as a colorless oil (652 mg, 96%). $[\alpha]_D^{20}$ +40° (c=1.9). ^{1}H-NMR δ: 0.72 (3H, d, J=6.5 Hz), 0.99 (3H, d, J=7 Hz), 1.37 (3H, s), 1.46 (3H, s), 1.69—2.05 (2H, m), 2.35 (1H, br s), 3.41—3.84 (5H, m). MS m/z (relative intensity): 173 ($M^+ - 15$, 13), 155 (1.5), 129 (8), 113 (10.5), 59 (100). Exact MS m/z Calcd for $C_9H_{17}O_3$ ($M^+ - 15$): 173.1179. Found: 173.1176.

A solution of dimethyl sulfoxide (DMSO) (746 μl, 10.5 mmol) in CH_2Cl_2 (4.0 ml) was added dropwise to a stirred CH_2Cl_2 solution (12 ml) of $(COCl)_2$ (459 μl, 5.26 mmol) cooled at −70 °C. After 10 min, the above pentanol (495 mg, 2.63 mmol) in CH_2Cl_2 (4.0 ml) was added dropwise, the stirring was continued for 30 min at −70 °C, and then Et_3N (1.5 ml, 10.8 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C, diluted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), and evaporated to leave an oil, which was chromatographed on a silica gel column (EtOAc–hexane, 1 : 1) to give **7** as a colorless oil (489 mg, 100%). $[\alpha]_D^{20}$ −5.0° (c=1.12). IR ν_{max} cm^{-1}: 1730. ^{1}H-NMR δ: 0.77 (3H, d, J=7 Hz), 1.15 (3H, d, J=7 Hz), 1.33 (3H, s), 1.44 (3H, s), 1.70—2.08 (1H, m), 2.47 (1H, ddq, J=1, 2.5, 7 Hz), 3.52 (1H, d, J=11.5 Hz), 3.76 (1H, dd, J=11.5, 5.5 Hz), 4.12 (1H, dd, J=10.5, 2.5 Hz), 9.66 (1H, d, J=1 Hz). MS m/z (relative intensity): 187 ($M^+ + 1$, 5.7), 171 (16), 149 (1.2), 59 (100). This unstable aldehyde (**7**) was immediately subjected to the coupling with **9**.

Diethyl (*S*)-3-Benzyloxymethyl-2-oxopentylphosphonate (9) A 1.6 M hexane solution of *n*-BuLi (0.527 ml) was added dropwise to a stirred ether solution (1.5 ml) of diethyl methylphosphonate (142 mg, 0.936 mmol) at −78 °C under argon. After 25 min, a solution of **8** (90 mg, 0.468 mmol) in ether (0.4 ml) was added dropwise. The reaction mixture was allowed to warm to −10 °C over a period of 1.5 h, quenched with saturated NH_4Cl, and extracted with ether. The extract was dried ($MgSO_4$) and evaporated, then the residue was chromatographed on a silica gel column (EtOAc–hexane, 4 : 1) to afford the hydroxyphosphonate as a colorless oil (138 mg, 85%). MS m/z (relative intensity): 344 (M^+, 0.6), 253 (3.8), 238 (7.5), 235 (7.6), 181 (100), 153 (20), 125 (43).

The above hydroxyphosphonate (138 mg, 0.40 mmol) was oxidized as described for **7** to afford **9** as a colorless oil (91 mg, 66%). IR ν_{max} cm^{-1}: 1710. ^{1}H-NMR δ: 0.89 (3H, t, J=7.5 Hz), 1.24—1.75 (8H, m), 2.90—3.27 (1H, m), 3.08 (1H, d, J=9.5 Hz), 3.31 (1H, d, J=9.5 Hz), 3.58 (2H, d, J=7.0 Hz), 3.98—4.28 (4H, m), 4.47 (2H, s), 7.30 (5H, s). MS m/z (relative intensity): 342 (M^+, 0.3), 324 (1.4), 251 (9.3), 236 (18), 207 (22), 91 (100). Exact MS m/z Calcd for $C_{17}H_{27}O_5P$ (M^+): 342.1598. Found: 342.1597.

(3*S*,7*S*,8*R*,9*S*)-3-Benzyloxymethyl-8,10-isopropylidenedioxy-7,9-dimethyldecan-4-one (10) A THF solution (1.5 ml) of **9** (553 mg, 1.62 mmol) was added dropwise to a stirred ice-cold suspension of NaH (32 mg, 1.37 mmol) in *N*,*N*-dimethylformamide (DMF) (0.5 ml) under argon. After 45 min, a solution of **7** (150 mg, 0.832 mmol) in THF (2.0 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature overnight, quenched with saturated NH_4Cl, and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated, and the residue was chromatographed on a silica gel column (ether–hexane, 1 : 1) to afford (3*S*,5*E*,7*S*,8*S*,9*S*)-3-benzyloxymethyl-8,10-isopropylidenedioxy-7,9-dimethyl-5-decen-4-one as a colorless oil (259 mg, 83%). $[\alpha]_D^{20}$ +11° (c=1.20). IR ν_{max} cm^{-1}: 1690, 1660, 1620. ^{1}H-NMR δ: 0.74 (3H, d, J=7 Hz), 0.86 (3H, t, J=7.5 Hz), 1.07 (3H, d, J=7.0 Hz), 1.35 (3H, s), 1.36 (3H, s), 1.41—1.91 (3H, m), 2.51—2.57 (1H, m), 3.09 (1H, ddq, J=13.5, 8, 7 Hz), 3.43—3.55 (3H, m), 3.65—3.77 (2H, m), 4.48 (2H, s), 6.18 (1H, d, J=15.5 Hz), 6.94 (1H, dd, J=15.5, 8 Hz), 7.30 (5H, m). MS m/z (relative intensity): 359 ($M^+ - 15$), 317 (0.8), 268 (1.3), 246 (5.5), 225 (1.6), 210 (3.1), 129 (94), 91 (100). Exact MS m/z Calcd for $C_{22}H_{31}O_4$ ($M^+ - 15$): 359.2224. Found: 359.2232.

A solution of the enone (665 mg, 1.82 mmol) in EtOAc (25 ml) was hydrogenated with 10% Pd–C (10 mg) to give **10** as a colorless oil (645 mg, 94%). $[\alpha]_D^{18}$ +30.0° (c=0.84). IR ν_{max} cm^{-1}: 1710. ^{1}H-NMR δ: 0.67 (3H, d, J=6.5 Hz), 0.85 (3H, d, J=7.5 Hz), 0.87 (3H, t, J=7.5 Hz), 1.33 (3H, s), 1.38 (3H, s), 1.40—1.84 (6H, m), 2.49 (2H, t, J=6.5 Hz), 2.80 (1H, tt, J=8, 5.5 Hz), 3.32—3.72 (5H, m), 4.47 (2H, s), 7.29 (5H, s), MS m/z (relative intensity): 376 (M^+, 0.2), 361 (5.3), 318 (1.5), 301 (2.1), 202 (7.0), 155 (7.1), 129 (25), 91 (100). Exact MS m/z Calcd for $C_{23}H_{36}O_4$ (M^+): 376.2616. Found; 376.2627.

(3*S*,4*R*,7*S*,8*R*,9*S*)-3-Benzyloxymethyl-8,10-isopropylidenedioxy-7,9-dimethyl-4-vinyldecan-4-ol (11) A THF solution (3.0 ml) of **10** (120 mg, 0.319 mmol) was added dropwise to a stirred Grignard reagent solution prepared from vinyl bromide (324 μl) and Mg (76 mg, 3.19 matom) in THF (10 ml) at −40 °C under argon. After 3 h, the reaction mixture was poured into cold saturated NH_4Cl, and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 5) to afford **11** as a colorless oil (125 mg, 97%). $[\alpha]_D^{19}$ +20° (c=1.00). ^{1}H-NMR δ: 0.67 (3H, d, J=7 Hz), 0.85 (3H, d, J=7 Hz), 0.94 (3H, t, J=7.5 Hz), 1.34 (3H, s), 1.40 (3H, s), 1.27—1.88 (10H, m), 3.44 (2H, d, J=11.5 Hz), 3.53—3.72 (3H, m), 4.39 (1H, d, J=11.5 Hz), 4.47 (1H, d, J=11.5 Hz), 5.12 (1H, dd, J=10.5, 2 Hz), 5.34 (1H, dd, J=17, 2 Hz), 5.89 (1H, dd, J=17, 10.5 Hz), 7.30 (5H, s). MS m/z (relative intensity): 389 ($M^+ - 15$, 1.2), 287 (0.6), 281

(0.6), 241 (4.9), 183 (27), 91 (100). Exact MS *m/z* Calcd for $C_{24}H_{37}O_4$ (M^+-15): 389.2694. Found: 389.2704.

(2*S*,3*R*,4*S*,7*S*,8*S*)-8-Benzyloxymethyl-1-(4-methoxybenzyloxy)-2,4-dimethyl-7-methyleneoxydecan-3-ol (12) A solution of **11** (57 mg, 0.141 mmol) in CH_2Cl_2 (6 ml) was ozonized at −78 °C for 20 min. After addition of $NaBH_4$ in MeOH, the reaction mixture was stirred for 15 min at −78 °C, then allowed to warm to room temperature, successively washed with 1 N HCl, 10% $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column (EtOAc–hexane, 2 : 3) to afford (3*S*,4*S*,7*S*,8*R*,9*S*)-3-benzyloxymethyl-4-hydroxymethyl-8,10-isopropylidenedioxy-7,9-dimethyldecan-4-ol as a colorless oil (40 mg, 70%). $[\alpha]_D^{18}$ +42° (c=1.44). ^{1}H-NMR δ: 0.68 (3H, d, J=7 Hz), 0.87 (3H, d, J=7 Hz), 0.93 (3H, t, J=7.5 Hz), 1.34 (3H, s), 1.39 (3H, s), 1.26—1.88 (9H, m), 2.49 (1H, t, J=6.5 Hz), 3.42—3.53 (5H, m), 3.65—3.80 (3H, m), 4.48 (1H, d, J=12 Hz), 4.57 (1H, d, J=12 Hz), 7.33 (5H, s), MS *m/z* (relative intensity): 393 (M^+-15, 1.1), 377 (0.8), 319 (0.4), 91 (100). Exact MS *m/z* Calcd for $C_{23}H_{37}O_5$ (M^+-15): 393.2643. Found: 393.2629.

MsCl (15 μl, 0.20 mmol) was added dropwise to a toluene solution (1 ml) of the above diol (77 mg, 0.189 mmol) and Et_3N (42 μl, 0.30 mmol) at 0 °C. After 2 h, CH_2Cl_2 (20 ml) and EtOH (0.5 ml) were added. The reaction mixture was stirred for 15 min at room temperature, washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 1) to afford the mesylate as a colorless oil (86 mg, 94%). $[\alpha]_D^{18.5}$ +21° (c=1.40). ^{1}H-NMR δ: 0.69 (3H, d, J=7 Hz), 0.87 (3H, d, J=7 Hz), 0.94 (3H, t, J=7 Hz), 1.34 (3H, s), 1.39 (3H, s), 1.51—2.01 (10H, m), 3.02 (3H, s), 3.39—3.86 (5H, m), 4.19 (2H, s), 4.03 (1H, s), 4.19 (1H, s), 7.33 (5H, s). MS *m/z* (relative intensity): 471 (M^+-15, 3.9), 91 (100). Exact MS *m/z* Calcd for $C_{24}H_{39}O_7S$ (M^+-15): 471.2419. Found: 471.2414.

A solution of the mesylate (84 mg, 0.173 mmol) in THF (5 ml) and 1 N HCl (2 ml) was stirred for 4 h at room temperature. The mixture was neutralized with $NaHCO_3$ and evaporated to remove THF. MeOH (5 ml) and K_2CO_3 (50 mg) were added to the aqueous solution, and the mixture was stirred vigorously for 1 h. After removal of precipitates, the filtrate was evaporated, and the residue was extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 1) to afford the epoxydiol as a colorless oil (61 mg, 100%). $[\alpha]_D^{17}$ +0.3° (c=0.76). ^{1}H-NMR δ: 0.77 (3H, d, J=7 Hz), 0.84 (3H, d, J=7 Hz), 0.93 (3H, t, J=7 Hz), 1.22—1.93 (10H, m), 2.43 (1H, br s), 2.61 (1H, d, J=4.5 Hz), 2.65 (1H, d, J=4.5 Hz), 3.41—3.77 (3H, m), 3.56 (2H, d, J=5.5 Hz), 4.49 (2H, s), 7.33 (5H, s). FD-MS *m/z* (relative intensity): 351 (M^++1, 100).

The epoxydiol (18 mg, 0.051 mmol) was added to a vigorously stirred suspension of NaH (5 mg) in DMSO (0.3 ml) at room temperature. After 10 min, MPM chloride (12 μl) was added, and the stirring was continued for 1 h. The reaction mixture was poured into cold saturated NH_4Cl, and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 3) to afford **12** as a colorless oil (22 mg, 91%). ^{1}H-NMR δ: 0.77 (3H, d, J=7 Hz), 0.83 (3H, d, J=7 Hz), 0.93 (3H, t, J=7 Hz), 1.26—2.10 (10H, m), 2.58 (1H, d, J=4.5 Hz), 2.66 (1H, d, J=4.5 Hz), 3.34—3.77 (5H, m), 3.80 (3H, s), 4.44 (2H, s), 4.49 (2H, s), 6.86 (2H, d, J=8.5 Hz), 7.20—7.31 (7H, m).

(2*R*,5*S*,6*R*)-2-[(*S*)-1-Benzyloxymethylpropyl]-6-[(*S*)-2-(4-methoxybenzyloxy)-1-methylethyl]-5-methyltetrahydropyran-2-carbaldehyde (13) A CH_2Cl_2 solution of **12** (57 mg, 0.121 mmol) and CSA (20 mg) was stirred at 0 °C for 20 min. After neutralization with Et_3N, the mixture was evaporated and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 4) to afford the alcohol as a colorless oil (47 mg, 83%), which was oxidized with $(COCl)_2$ and DMSO as described for **7** to afford **13** as a colorless oil (47 mg, 100%). $[\alpha]_D^{19}$ −56° (c=1.48). IR ν_{max} cm^{-1}: 1730, 1620, 1590. ^{1}H-NMR δ: 0.87 (3H, t, J=7.5 Hz), 0.90 (3H, d, J=7 Hz), 0.93 (3H, d, J=7 Hz), 1.45—1.80 (8H, m), 2.15—2.20 (1H, m), 3.37—3.76 (5H, m), 3.78 (3H, s), 4.31 (1H, d, J=11 Hz), 4.38 (1H, d, J=11 Hz), 4.39 (1H, d, J=12 Hz), 4.49 (1H, d, J=12 Hz), 6.86 (2H, d, J=9 Hz), 7.17—7.37 (7H, m), 9.50 (1H, s). MS *m/z* (relative intensity): 439 (M^+-29, 1.3), 377 (1.7), 331 (0.6), 329 (1.7), 121 (100). Exact MS *m/z* Calcd for $C_{28}H_{39}O_4$ (M^+-29): 439.2851. Found: 439.2845.

(*S*)-1-Benzyloxy-2-[(2*R*,5*S*,6*R*)-6-[(*S*)-1-(4-methoxybenzyloxymethyl)ethyl]-5-methyltetrahydropyran-2-yl]butane (14) An MeCN solution (0.5 ml) of **13** (15 mg, 0.032 mmol) and $(Ph_3P)_3RhCl$ (94 mg, 0.102 mmol) was heated at 160 °C in a sealed tube for 9 h. After evaporation of the solvent, the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 3) to give the starting material **13** (1 mg, 7%) and **14** as a colorless oil (4 mg, 28%). $[\alpha]_D^{13}$ −40° (c=0.08). ^{1}H-NMR δ: 0.87 (3H, t, J=8 Hz), 0.89 (3H, d, J=7 Hz), 0.96 (3H, d, J=7 Hz), 1.23—2.17 (9H, m), 3.29—3.45 (2H, m), 3.49—3.57 (3H, m), 3.77 (3H, s), 3.78—3.83 (1H, m), 4.31 (1H, d, J=11.5 Hz), 4.38 (1H, d, J=11.5 Hz), 4.41 (1H, d, J=12 Hz), 4.48 (1H, d, J=12 Hz), 6.84 (2H, d, J=8.5 Hz), 7.21 (2H, d, J=8.5 Hz), 7.31 (5H, s). MS *m/z* (relative intensity): 349 (M^+-91, 3.0), 319 (2.5), 304 (1.1), 121 (100), 91 (57). Exact MS *m/z* Calcd for $C_{21}H_{33}O_4$ (M^+-91): 349.2381. Found: 349.2379. Calcd for $C_{20}H_{31}O_3$ (M^+-121): 319.2275. Found: 319.2260.

(*S*)-2-[(2*R*,3*S*,6*R*)-6-[(*S*)-1-Benzyloxymethylpropyl]-3-methyltetrahydropyran-2-yl]propan-1-ol (15) A solution of **14** (19 mg, 0.043 mmol) and DDQ (11 mg, 0.048 mmol) in CH_2Cl_2 (0.4 ml) and water (20 μl) was stirred for 1 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 ml), washed with 10% $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica gel column (EtOAc–benzene, 1 : 11) to afford **15** as a colorless oil (14 mg, 100%). $[\alpha]_D^{19}$ −32° (c=1.40). ^{1}H-NMR δ: 0.73 (3H, d, J=7 Hz), 0.89 (3H, t, J=7.5 Hz), 0.99 (3H, d, J=7.5 Hz), 1.06—1.32 (4H, m), 1.36—1.99 (4H, m), 2.08—2.24 (1H, m), 3.34—3.75 (6H, m), 3.83 (1H, dd, J=10.5, 5 Hz), 4.46 (1H, d, J=12 Hz), 4.60 (1H, d, J=12 Hz), 7.28—7.39 (5H, m). MS *m/z* (relative intensity): 320 (M^+, 1.0), 302 (2.5), 273 (1.8), 261 (3.8), 229 (3.6), 157 (27), 91 (100). *Anal.* Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.85; H, 10.03. Exact MS *m/z* Calcd for $C_{20}H_{32}O_3$ (M^+): 320.2353. Found: 320.2338.

(*S*)-2-[(2*R*,5*S*,6*R*)-6-[(*S*)-1-(4-Methoxybenzyloxymethyl)ethyl]-5-methyltetrahydropyran-2-yl]butan-1-ol (16) An EtOH solution of **14** (12 mg, 0.027 mmol) was hydrogenated over Raney Ni (W-4) at ordinary temperature and pressure for 2 h. After removal of the catalyst, the filtrate was evaporated and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 3) to afford **16** as a colorless oil (9 mg, 96%). $[\alpha]_D^{16}$ −31° (c=1.16). ^{1}H-NMR δ: 0.92 (3H, t, J=7.5 Hz), 0.92 (3H, d, J=7 Hz), 0.96 (3H, d, J=7 Hz), 1.17—1.37 (2H, m), 1.42—1.54 (2H, m), 1.65—2.10 (5H, m), 2.27 (1H, t, J=6.5 Hz), 3.36—3.78 (6H, m), 3.80 (3H, s), 4.39 (1H, d, J=11.5 Hz), 4.49 (1H, d, J=11.5 Hz), 6.87 (2H, d, J=9 Hz), 7.27 (2H, d, J=9 Hz). MS *m/z* (relative intensity): 350 (M^+, 0.6), 229 (3.7), 217 (4.0), 214 (5.2), 121 (100). Exact MS *m/z* Calcd for $C_{21}H_{34}O_4$ (M^+): 350.2459. Found: 350.2447.

(*R*)-2-[(2*R*,5*S*,6*R*)-6-[(*R*)-1-Formylethyl]-5-methyltetrahydropyran-2-yl]butanoic Acid (2) a) From **15**: Compound **15** (1.1 g, 3.43 mmol) was oxidized with $(COCl)_2$ and DMSO as described for **7** to afford the aldehyde (934 mg, 85%), $[\alpha]_D^{19}$ −75° (c=0.8). IR ν_{max} cm^{-1}: 1730, 1500. ^{1}H-NMR δ: 0.87 (3H, t, J=7.5 Hz), 0.95 (3H, d, J=7.5 Hz), 0.99 (3H, d, J=8 Hz), 1.25—1.53 (4H, m), 1.80—1.90 (3H, m), 1.99—2.04 (1H, m), 2.53 (1H, ddq, J=10, 3, 8 Hz), 3.37 (1H, dd, J=9.5, 5.5 Hz), 3.51 (1H, dd, J=9.5, 3.5 Hz), 3.72 (1H, dt, J=10, 4.5 Hz), 3.81 (1H, dd, J=10, 2.5 Hz), 4.43 (1H, d, J=11.5 Hz), 4.50 (1H, d, J=11.5 Hz), 7.24—7.35 (5H, m), 9.64 (1H, d, J=3 Hz). MS *m/z* (relative intensity): 318 (M^+, 0.6), 290 (0.4), 260 (1.4), 227 (1.7), 219 (2.0), 212 (5.8), 169 (5.6), 91 (100). Exact MS *m/z* Calcd for $C_{20}H_{30}O_3$ (M^+): 318.2197. Found: 318.2215. *Anal.* Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found; C, 74.94; H, 9.57.

A solution of the aldehyde (914 mg, 2.87 mmol), $(CH_2OH)_2$ (1.3 ml), and TsOH (90 mg) in benzene (70 ml) was refluxed in a Dean–Stark apparatus (for removal of water) for 1.5 h. The reaction mixture was cooled to room temperature, washed with 10% $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated to give the acetal as a colorless oil (1.04 g, 100%). $[\alpha]_D^{19}$ −68° (c=1.40). ^{1}H-NMR δ: 0.75 (3H, d, J=7 Hz), 0.89 (3H, t, J=7.5 Hz), 0.97 (3H, d, J=7 Hz), 1.26—1.46 (4H, m), 1.80—2.23 (5H, m), 3.51—3.95 (8H, m), 4.47 (1H, d, J=12 Hz), 4.54 (1H, d, J=12 Hz), 5.10 (1H, d, J=2 Hz), 7.25—7.35 (5H, m). MS *m/z* (relative intensity): 362 (M^+, 1.5), 300 (1.0), 271 (1.4), 91 (72), 73 (100). Exact MS *m/z* Calcd for $C_{22}H_{34}O_4$ (M^+): 362.2459. Found 362.2462.

A solution of the acetal (103 mg, 0.284 mmol) in EtOAc (3 ml) was hydrogenated with 10% Pd–C (50 mg) at ordinary temperature and pressure for 15 h. Work up gave (*S*)-2-[(2*R*,5*S*,6*R*)-6-[(*R*)-1-(2,2-ethylenedioxymethyl)ethyl]-5-methyltetrahydropyran-2-yl]butan-1-ol as a colorless oil (64 mg, 83%), mp 56—56.5 °C (colorless prisms from hexane). $[\alpha]_D^{18}$ +43° (c=0.76). ^{1}H-NMR δ: 0.81 (3H, d, J=7 Hz), 0.93 (3H, t, J=7 Hz), 0.98 (3H, d, J=7 Hz), 1.28 (2H, quintet, J=7 Hz), 1.44—1.49 (2H, m), 1.74—2.11 (5H, m), 3.60 (1H, br s), 3.61 (1H, dd, J=10.5, 2 Hz), 3.70—4.25 (7H, m), 5.08 (1H, d, J=3 Hz). MS *m/z* (relative intensity): 272 (M^+, 0.9), 199 (8.5), 73 (100). Exact MS *m/z* Calcd for $C_{15}H_{28}O_4$ (M^+): 272.1989. Found: 272.1975. *Anal.* Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.19; H, 10.17.

A solution of the alcohol (44 mg, 0.162 mmol) in acetone (5 ml) was oxidized with 2.6 M Jones reagent (0.5 ml) at 0 °C for 40 min. The reaction mixture was quenched with iso-PrOH, diluted with ether, washed with brine, dried ($MgSO_4$), and evaporated to give (*R*)-2-[(2*R*,5*S*,6*R*)-6-[(*R*)-1-(2,2-ethylenedioxymethyl)ethyl]-5-methyltetrahydropyran-2-yl]butanoic acid as a colorless solid (38 mg, 82%). $[\alpha]_{\mathrm{D}}^{16}$ $-67°$ ($c=0.80$). IR $\nu_{\max}$ cm^{-1}: 1730, 1710. ^{1}H-NMR δ: 0.79 (3H, d, $J=7$ Hz), 0.96 (3H, t, $J=7.5$ Hz), 0.96 (3H, d, $J=7$ Hz), 1.43—1.69 (4H, m), 1.77—1.94 (4H, m), 2.29 (1H, ddd, $J=8.5$, 7.5, 6.5 Hz), 3.71 (1H, dd, $J=10.5$, 2 Hz), 3.82—4.08 (5H, m), 5.00 (1H, d, $J=2$ Hz), MS *m/z* (relative intensity); 286 (M^+, 2.2), 199 (2.9), 113 (14), 73 (100). Exact MS *m/z* Calcd for $C_{15}H_{26}O_5$ (M^+): 286.1782. Found: 286.1786.

A solution of the acid (20 mg, 0.07 mmol) in THF (1 ml) and 2 N HCl (0.5 ml) was stirred at room temperature for 4 h. The reaction mixture was extracted with ether, and the extract was washed with brine, dried (Na_2SO_4), and evaporated to leave **2** as a colorless solid (15 mg, 91%). $[\alpha]_{\mathrm{D}}^{17}$ $-58°$ ($c=0.60$). ^{1}H-NMR δ: 0.94—1.02 (9H, m), 1.26—1.60 (4H, m), 1.63—1.96 (3H, m), 2.40 (1H, ddq, $J=10$, 3.5, 7 Hz), 2.92 (2H, dt, $J=4$, 10 Hz), 8.65 (1H, br s), 9.60 (1H, d, $J=3.5$ Hz). MS *m/z* (relative intensity): 242 (M^+, 0.7), 196 (14), 167 (16), 82 (100). Exact MS *m/z* Calcd for $C_{13}H_{22}O_4$ (M^+): 242.1519. Found: 242.1500.

b) From **16**: A solution of **16** (31 mg, 0.088 mmol) in acetone (4 ml) was oxidized with 2.6 M Jones reagent (0.3 ml) as described above to give the acid as a colorless oil (25 mg, 77%), $[\alpha]_{\mathrm{D}}^{17.5}$ $-56°$ ($c=1.56$). IR $\nu_{\max}$ cm^{-1}: 1700, 1610, 1580. ^{1}H-NMR δ: 0.89 (3H, d, $J=6.5$ Hz), 0.95 (3H, t, $J=7$ Hz), 0.94 (3H, d, $J=7$ Hz), 1.45—1.53 (4H, m), 1.76—2.17 (4H, m), 2.89—3.02 (1H, m), 3.24 (1H, t, $J=9$ Hz), 3.50 (1H, dd, $J=10$, 2 Hz), 3.63 (1H, dd, $J=9$, 3.5 Hz), 3.79 (3H, s), 3.88—4.05 (1H, m), 4.39 (2H, s), 6.86 (2H, d, $J=8.5$ Hz), 7.28 (2H, d, $J=8.5$ Hz). MS *m/z* (relative intensity): 364 (M^+, 1.0), 243 (1.6), 227 (12), 121 (100). Exact MS *m/z* Calcd for $C_{21}H_{32}O_5$ (M^+): 364.2251. Found: 364.2245.

A solution of the acid (22 mg, 0.06 mmol) in EtOAc (1 ml) was hydrogenated with 10% Pd–C (6 mg) as described above to give the alcohol as a viscous oil (13 mg, 86%). $[\alpha]_{\mathrm{D}}^{18}$ $-42°$ ($c=0.76$). IR $\nu_{\max}$ cm^{-1}: 1720, 1700. ^{1}H-NMR δ: 0.76 (3H, d, $J=7.5$ Hz), 9.97 (3H, d, $J=6$ Hz), 0.98 (3H, t, $J=6.5$ Hz), 1.13—1.67 (4H, m), 1.81—2.07 (4H, m), 2.99 (1H, dt, $J=4.5$, 10 Hz), 3.51—3.60 (2H, m), 3.67 (1H, dd, $J=10.5$, 2 Hz), 4.03 (1H, dd, $J=10.5$, 5 Hz). MS *m/z* (relative intensity): 244 (M^+, 1.6), 226 (6.7), 185 (31), 167 (63), 69 (100). Exact MS *m/z* Calcd for $C_{13}H_{24}O_4$ (M^+): 244.1676. Found: 244.1676.

Powdered molecular sieves 3 Å (10 mg) and PCC (22 mg) were added to a stirred CH_2Cl_2 solution (1 ml) of the alcohol (13 mg, 0.054 mmol) at room temperature. After 1.2 h, the reaction mixture was diluted with ether (5 ml). The supernatant was dried ($MgSO_4$), and evaporated, and the residue was subjected to TLC on silica gel (MeOH–CH_2Cl_2, 1 : 10) to afford **2** (8 mg, 67%).

6-*O*-(*tert*-Butyldimethylsilyl)-3,5-dideoxy-5-*C*-ethyl-1,2-*O*-isopropylidene-3-*C*-methyl-*β*-L-allofuranose (18) A 1.25 M ether solution of MeLi (55 ml) was added dropwise to a stirred suspension of CuI (7.4 g, 39 mmol) in ether (90 ml) at -25 °C under argon. After 30 min, **17** (3.9 g, 7.79 mmol) in ether (40 ml) was added dropwise. The mixture was stirred at 0 °C for 45 min and at room temperature for 2 h, then poured into aqeous NH_4Cl, and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 3) to afford **18** as a colorless oil (2.5 g, 94%). ^{1}H-NMR δ: 0.05 (6H, s), 0.90 (9H, s), 0.92 (3H, t, $J=6.5$ Hz), 1.05 (3H, d, $J=7$ Hz), 1.32 (3H, s), 1.50 (3H, s), 1.26—1.57 (2H, m), 1.80—2.10 (2H, m), 3.56 (1H, dd, $J=9.5$, 7 Hz), 3.71 (1H, dd, $J=9.5$, 5 Hz), 3.96 (1H, dd, $J=10.5$, 2.5 Hz), 4.52 (1H, t, $J=4.5$ Hz), 5.73 (1H, d, $J=3.5$ Hz). MS *m/z* (relative intensity): 329 (M^+-15, 6.9), 287 (1.2), 229 (1.4), 199 (57), 159 (40), 75 (100).

(2*R*,3*R*,4*S*)-4-Benzyloxymethyl-3-formyloxy-2-methylhexanal (19) A solution of **18** (2.5 g, 7.26 mmol) in MeOH (30 ml) and 1 N HCl (7 ml) was stirred at room temperature for 20 min. After neutralization with $NaHCO_3$, the mixture was evaporated and the residue extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and evaporated, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 3) to afford the alcohol as a colorless oil (1.6 g, 97%). ^{1}H-NMR δ: 0.97 (3H, t, $J=7.5$ Hz), 1.05 (3H, d, $J=7$ Hz), 1.12—1.60 (3H, m), 1.33 (3H, s), 1.51 (3H, s), 1.90—2.08 (1H, m), 2.30 (1H, t, $J=5.5$ Hz), 3.40—3.80 (2H, m), 3.98 (1H, dd, $J=10.5$, 2.5 Hz), 4.53 (1H, t, $J=4.5$ Hz), 5.75 (1H, d, $J=4$ Hz). MS *m/z* (relative intensity): 215 (M^+-15, 34), 157 (52), 99 (75), 59 (100). Exact MS *m/z* Calcd for $C_{11}H_{19}O_4$ (M^+-15): 215.1285. Found: 215.2174.

A solution of the alcohol (1.6 g, 6.95 mmol) in THF (5 ml) was added to a stirred suspension of NaH (333 mg, 13.9 mmol) in DMSO (15 ml) at room temperature. After evolution of hydrogen had ceased, BnCl (1.4 g, 11.1 mmol) was added under argon. After 7 h, work-up in the usual way gave the Bn ether as a colorless oil (2.0 g, 90%). $[\alpha]_{\mathrm{D}}^{20}$ $+41°$ ($c=0.28$). ^{1}H-NMR δ: 0.93 (3H, t, $J=7.5$ Hz), 1.05 (3H, d, $J=7$ Hz), 1.33 (3H, s), 1.51 (3H, s), 1.38—2.08 (4H, m), 3.45 (1H, dd, $J=4$, 1.5 Hz), 3.56 (1H, d, $J=4$ Hz), 3.98 (1H, dd, $J=10.5$, 2.5 Hz), 4.50 (1H, d, $J=4$ Hz), 4.51 (1H, t, $J=4.5$ Hz), 4.54 (1H, d, $J=4$ Hz), 5.73 (1H, d, $J=3.5$ Hz), 7.32 (5H, s). MS *m/z* (relative intensity): 320 (M^+, 0.9), 305 (2.8), 262 (2.0), 245 (2.1), 220 (3.1), 90 (100). *Anal.* Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.06; H, 8.86.

A solution of the Bn ether (1.9 g, 5.45 mmol) in THF (35 ml) and 4 N HCl (10 ml) was stirred at 45 °C for 8 h. After neutralization with $NaHCO_3$ and evaporation of the solvent, the residue was extracted with CH_2Cl_2. The extract was evaporated, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 2 : 3) to afford the lactol (1.5 g, 98%). $NaIO_4$ (813 mg, 3.82 mmol) was added to a stirred solution of the lactol (580 mg, 2.07 mmol) in THF (10 ml) and MeOH (10 ml) at room temperature. After 1 h, precipitates was removed and the filtrate was concentrated. The residue was extracted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), and evaporated to give **19** as a colorless oil (570 mg, 99%). IR $\nu_{\max}$ cm^{-1} 1720. ^{1}H-NMR δ: 0.92 (3H, t, $J=7.5$ Hz), 1.12 (3H, d, $J=7$ Hz), 1.26—2.09 (3H, m), 2.75 (1H, ddq, $J=6$, 2.5, 7 Hz), 3.34 (1H, dd, $J=9.5$, 6.5 Hz), 3.51 (1H, dd, $J=9.5$, 4 Hz), 4.44 (2H, s), 5.47 (1H, t, $J=6$ Hz), 7.32 (5H, s), 8.10 (1H, s), 9.65 (1H, d, $J=2.5$ Hz).

(2*Z*,4*S*,5*S*,6*S*)-6-Benzyloxymethyl-2,4-dimethyloct-2-en-5-olide (20) A THF solution (6 ml) of dimethyl 1-methoxycarbonylethylphosphonate (1.1 g, 5.61 mmol) was added dropwise to a stirred suspension of NaH (115 mg, 4.79 mmol) in THF (6 ml) at 0 °C. The mixture was stirred at 0 °C for 10 min and at room temperature for 30 min, and then cooled at -85 °C. A solution of **19** (550 mg, 1.98 mmol) in THF (6 ml) was added dropwise to the solution below -78 °C under argon. The reaction mixture was allowed to warm to -15 °C over a period of 3 h, then poured into cold aqueous NH_4Cl, and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated to leave an oil, which was dissolved in MeOH (10 ml). After addition of K_2CO_3 (350 mg), the reaction mixture was stirred for 30 min at room temperature, and evaporated. The residue was extracted with ether, the extract was evaporated, and this residue was chromatographed on a silica gel column (EtOAc–hexane, 1 : 5) to afford **20** as a colorless oil (421 mg, 74%). $[\alpha]_{\mathrm{D}}^{20}$ $+82°$ ($c=0.80$). IR $\nu_{\max}$ cm^{-1}: 1710. ^{1}H-NMR δ: 0.95 (3H, t, $J=7.5$ Hz), 1.07 (3H, d, $J=7$ Hz), 1.23—1.95 (3H, m), 1.91 (3H, d, $J=1.5$ Hz), 2.60—2.72 (1H, m), 3.52—3.66 (2H, m), 4.33 (1H, dd, $J=10$, 2 Hz), 4.48 (1H, d, $J=12.5$ Hz), 4.55 (1H, d, $J=12.5$ Hz), 6.33—6.36 (1H, m), 7.32 (5H, s). MS *m/z* (relative intensity): 289 (M^++1, 0.2), 193 (3.8), 127 (61), 91 (100). Exact MS *m/z* Calcd for $C_{18}H_{25}O_3$ (M^++1): 289.1805. Found: 289.1812.

(*S*)-1-Benzyloxy-2-[(2*S*,3*S*,6*S*)-2,3-dihydro-6-isopropyloxy-3,5-dimethylpyran-2-yl]butane (21) A 1.73 M toluene solution of DIBAH (0.74 ml) was added dropwise to a stirred toluene solution (6 ml) of **20** (353 mg, 1.22 mmol) at -80 °C under argon. After 10 min, the reaction mixture was quenched with MeOH, diluted with ether, and filtered through celite. The filtrate was washed with brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in iso-PrOH (7 ml) containing CSA (30 mg), and this solution was stirred for 15 min at room temperature, then neutralized with Et_3N, and evaporated. The residue was chromatographed on silica gel (EtOAc–hexane, 1 : 4) to afford **21** as a colorless oil (370 mg, 91%). $[\alpha]_{\mathrm{D}}^{18}$ $+98°$ ($c=0.80$). ^{1}H-NMR δ: 0.92 (3H, d, $J=7.5$ Hz), 0.96 (3H, t, $J=7.5$ Hz), 1.15 (3H, d, $J=6.5$ Hz), 1.17—1.64 (2H, m), 1.18 (3H, d, $J=6.5$ Hz), 1.69—1.83 (1H, m), 1.68 (3H, br s), 2.21—2.42 (1H, m), 3.49—3.61 (2H, m), 3.76 (1H, dd, $J=10.5$, 1.5 Hz), 3.97 (1H, septet, $J=6.5$ Hz), 4.47 (1H, d; $J=12$ Hz), 4.55 (1H, d, $J=12$ Hz), 4.78 (1H, s), 5.43 (1H, br s), 7.27—7.34 (5H, m). MS *m/z* (relative intensity): 272 (M^+-60, 6.2), 181 (43), 109 (100), 98 (37), 91 (82). Exact MS *m/z* Calcd for $C_{18}H_{24}O_2$ (M^+-60): 272.1788. Found: 272.1788. *Anal.* Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.81; H, 9.64.

(*S*)-2-[(2*S*,3*S*,5*R*,6*S*)-6-Isopropyloxy-3,5-dimethyltetrahydropyran-2-yl]butan-1-ol (22) An EtOH solution of **21** (170 mg, 0.51 mmol) was hydrogenated over Raney Ni (W-2) at ordinary temperature and pressure for 2 h. After removal of the catalyst and the solvent, the residue was dissolved in ether (4.5 ml) and hydrogenated over 5% Rh–Al_2O_3 (45 mg) for 3.5 h. Work-up and chromatography on a silica gel column (EtOAc–hexane, 1 : 5) gave **22** as a colorless oil (103 mg, 82%). $[\alpha]_{\mathrm{D}}^{18}$ $+169°$ ($c=0.8$). ^{1}H-NMR δ: 0.78 (3H, d, $J=6.5$ Hz), 0.82 (3H, d, $J=6.5$ Hz), 0.90 (3H, t, $J=7.5$ Hz), 1.09 (3H, d, $J=6$ Hz), 1.23 (3H, d, $J=6$ Hz), 1.24—1.90 (7H, m), 2.91—3.10 (1H, m), 3.68—3.95 (4H, m), 4.64 (1H, d, $J=3$ Hz). MS *m/z* (relative intensity): 244 (M^+, 0.2), 202 (8.8), 184 (14), 100 (100), 87 (78). Exact MS *m/z* Calcd for $C_{14}H_{28}O_3$ (M^+): 244.2040. Found: 244.2013. Acetate: $[\alpha]_{\mathrm{D}}^{18}$ $+158°$ ($c=1.36$). ^{1}H-NMR δ: 0.80 (3H, d, $J=6.5$ Hz), 0.81

(3H, d, $J=7$ Hz), 0.96 (3H, t, $J=7.5$ Hz), 1.07 (3H, d, $J=6$ Hz), 1.16 (3H, d, $J=6$ Hz), 1.22—1.83 (7H, m), 2.05 (3H, s), 3.58 (1H, dd, $J=9.5$, 1.5 Hz), 3.80 (1H, septet, $J=6$ Hz), 4.00 (1H, dd, $J=10.5$, 9 Hz), 4.21 (1H, dd, $J=10.5$, 5 Hz), 4.62 (1H, d, $J=3.5$ Hz).

(2*R*,4*S*)-4-[(2*S*,3*S*,5*R*,6*S*)-6-Isopropyloxy-3,5-dimethyltetrahydropyran-2-yl]hexan-3-ol (23) Compound **22** (181 mg, 0.74 mmol) was oxidized as described for **7** to give the aldehyde as a colorless oil (180 mg, 100%). IR ν_{max} cm^{-1}: 1730. ^{1}H-NMR δ: 0.82 (3H, d, $J=7$ Hz), 0.83 (3H, d, $J=6.5$ Hz), 0.96 (3H, t, $J=7.5$ Hz), 1.05 (3H, d, $J=6$ Hz), 1.15 (3H, d, $J=6$ Hz), 1.21—1.93 (6H, m), 2.24—2.29 (1H, m), 3.71 (1H, septet, $J=6$ Hz), 3.93 (1H, dd, $J=10.5$, 2.5 Hz), 4.58 (1H, d, $J=3.5$ Hz), 9.70 (1H, d, $J=2$ Hz).

An ether solution (5 ml) of the aldehyde (180 mg, 0.74 mmol) was added dropwise to a Grignard solution prepared from EtBr (830 mg, 11.1 mmol) and Mg (180 mg, 7.71 matom) in ether (12 ml) at −50 °C. After 1 h, the reaction mixture was allowed to warm to 0 °C during 30 min, poured into cold aqueous NH_4Cl, and extracted with ether. The extract was dried ($MgSO_4$), and evaporated, and the residue was chromatographed on a silica gel column (EtOAc–hexane, 1:10) to afford **23** as a colorless oil (179 mg, 89%). $[\alpha]_D^{17}$ +149° ($c=0.52$). Acetate: ^{1}H-NMR δ: 0.78 (3H, d, $J=6$ Hz), 0.81 (3H, d, $J=6.5$ Hz), 0.86 (3H, t, $J=7.5$ Hz), 0.96 (3H, t, $J=7.5$ Hz), 1.08 (3H, d, $J=6.5$ Hz), 1.19 (3H, d, $J=6.5$ Hz), 1.02—1.96 (9H, m), 2.05 (3H, s), 3.56 (1H, dd, $J=9.5$, 1.5 Hz), 3.80 (1H, septet, $J=6.5$ Hz), 4.60 (1H, d, $J=3.5$ Hz), 5.01 (1H, dt, $J=8$, 3.5 Hz). MS *m/z* (relative intensity): 314 (M^+, 0.5), 272 (4.2), 254 (5.3), 195 (5.9), 100 (100). Exact MS *m/z* Calcd for $C_{18}H_{34}O_4$ (M^+): 314.2459. Found: 314.2431.

(2*R*,4*S*,5*S*,6*R*)-6-Ethyl-2,4-dimethyl-7-oxononan-5-olide (3) A solution of **23** (16 mg, 0.059 mmol) in THF (3 ml) and 4 N HCl (1 ml) was stirred at 45 °C for 15 min. Work-up gave the lactol (13 mg, 96%). MS *m/z* (relative intensity): 212 (M^+-18, 6.0), 188 (4.5), 183 (6.7), 172 (5.6), 165 (4.9), 154 (20), 57 (100). Exact MS *m/z* Calcd for $C_{13}H_{24}O_2$ (M^+-18): 212.1778. Found: 212.1774.

A CH_2Cl_2 solution (2 ml) of the lactol (12 mg, 0.052 mmol) was stirred with powdered molecular sieves 3 Å (60 mg) and PCC (67 mg) at room temperature for 4 h. Work-up and chromatography on a silica gel column (EtOAc–hexane, 1:3) gave **3** as a colorless oil (12 mg, 100%). $[\alpha]_D^{15}$ +18° ($c=0.44$). IR ν_{max} cm^{-1}: 1730. ^{1}H-NMR δ: 0.92 (3H, t, $J=7.5$ Hz), 1.00 (3H, d, $J=7$ Hz), 1.06 (3H, t, $J=7$ Hz), 1.27 (3H, d, $J=7.5$ Hz), 1.34—2.04 (5H, m), 2.57 (2H, q, $J=7.5$ H), 2.38—2.67 (2H, m), 4.27 (1H, dd, $J=9.5$, 4 Hz). MS *m/z* (relative intensity): 226 (M^+, 1.5), 197 (6.3), 57 (100). Exact MS *m/z* Calcd for $C_{13}H_{22}O_3$ (M^+): 226.1570. Found: 226.1562.

(2*R*,4*S*,5*S*,6*S*,7*R*)-6-Ethyl-5,7-isopropylidenedioxy-2,4-dimethyl-1-(4-nitrobenzoyloxy)nonane (24) Compound **23** (25 mg, 0.092 mmol) was hydrolyzed with HCl as described above to give the lactol (25 mg), which was reduced with $LiAlH_4$ (15 mg) to give the alcohol (15 mg). An acetone solution (1 ml) of the alcohol (15 mg), 2,2-dimethoxypropane (0.1 ml), and CSA (3 mg) was stirred for 30 min at room temperature to give the acetonide (11 mg), which was treated with 4-nitrobenzoyl chloride (16 mg), Et_3N (8 mg), and DMAP (2 mg) for 1.5 h at room temperature. The reaction mixture was evaporated and the residue was chromatographed on an alumina column (EtOAc–hexane, 1:3) to afford **24** as a colorless viscous oil (19 mg). ^{1}H-NMR δ: 0.87 (3H, d, $J=6.5$ Hz), 0.96 (3H, t, $J=7.5$ Hz), 0.97 (3H, t, $J=7.5$ Hz), 1.06 (3H, d, $J=7$ Hz), 1.29 (3H, s), 1.36 (3H, s), 1.26—1.93 (8H, m), 2.06—2.16 (1H, m), 3.34 (1H, dd, $J=9.5$, 1.5 Hz), 3.67 (1H, ddd, $J=6.5$, 6, 2 Hz), 4.12 (1H, dd, $J=11$, 7 Hz), 4.31 (1H, dd $J=11$, 5 Hz), 8.22 (2H, d, $J=8.5$ Hz), 8.27 (2H, d, $J=8.5$ Hz).

(2*R*,4*S*,5*S*,6*S*,7*R*)-6-Ethyl-7-(4-methoxybenzyloxy)-2,4-dimethylnonan-5-olide (25) A THF solution (0.4 ml) of **23** (65 mg, 0.239 mmol) was added to a stirred suspension of NaH (14 mg, 0.583 mmol) in DMF (0.1 ml) at room temperature. After evolution of H_2 had ceased, MPM chloride (70 μl, 0.497 mmol) was added, and the mixture was stirred at 50 °C for 18 h under argon. Et_2NH (0.4 ml) was added to decompose excess MPM chloride, and the mixture was poured into cold saturated NH_4Cl and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane–EtOAc, 16:1) to afford an MPM ether as a colorless oil (81 mg, 86%). $[\alpha]_D^{18}$ +93° ($c=0.92$). ^{1}H-NMR δ: 0.81 (6H, d, $J=7.0$ Hz), 0.92 (3H, t, $J=7.5$ Hz), 0.97 (3H, t, $J=7.5$ Hz), 1.07 (3H, d, $J=6.5$ Hz), 1.17 (3H, d, $J=6.5$ Hz), 1.23—1.74 (9H, m), 3.42 (1H, dt, $J=7.0$, 3.5 Hz), 3.59 (1H, d, $J=11.0$ Hz), 3.80 (3H, s), 3.81 (1H, septet, $J=6.5$ Hz), 4.44 (2H, s), 4.60 (1H, d, $J=3.0$ Hz), 6.86 (2H, d, $J=8.5$ Hz), 7.28 (2H, d, $J=8.5$ Hz). MS *m/z* (relative intensity): 332 (M^+-119, 0.7), 303 (0.3), 259 (0.6), 256 (0.9), 250 (0.7), 211 (2.9), 121 (100). Exact MS *m/z* Calcd for $C_{21}H_{32}O_3$ (M^+-119): 332.2353. Found: 332.2355.

A 0.4 N HCl solution (0.5 ml) was added to a THF solution (1 ml) of the above oil (55 mg, 0.14 mmol) and the reaction mixture was stirred at 55 °C for 16 h, neutralized with $NaHCO_3$ and then extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane–EtOAc, 4:1) to afford a colorless oil (40 mg, 80%).

The oil (31 mg, 0.088 mmol) was dissolved in CH_2Cl_2 (1 ml), and oxidized with PCC (38 mg, 0.177 mmol) and 3 Å molecular sieves (39 mg) at room temperature for 2 h. Work-up and chromatography on a silica gel column (*n*-hexane–EtOAc, 3:1) gave **25** as a colorless solid (29 mg, 94%). $[\alpha]_D^{17}$ +56° ($c=1.16$). IR ν_{max} cm^{-1}: 1720. ^{1}H-NMR δ: 0.90—0.99 (9H, m), 1.26 (3H, d, $J=7.5$ Hz), 1.26—1.90 (8H, m), 2.19—2.59 (1H, m), 3.44—3.46 (1H, m), 3.80 (3H, s), 4.24 (1H, d, $J=10.5$ Hz), 4.39 (1H, d, $J=11.0$ Hz), 4.47 (1H, d, $J=11.0$ Hz), 6.87 (2H, d, $J=8.5$ Hz), 7.26 (2H, d, $J=8.5$ Hz). MS *m/z*: 348 (M^+, 2.5), 264 (1.1), 212 (6.0), 121 (100). Exact MS *m/z* Calcd for $C_{21}H_{32}O_4$ (M^+): 348.2302. Found: 348.2291. *Anal.* Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 71.81; H, 9.51.

(3*S*, 4*S*)-4-[(2*S*,3*S*,5*R*,6*S*)-6-Isopropyloxy-3,5-dimethyltetrahydropyran-2-yl]hexan-3-ol (26) Compound **23** (90 mg, 0.33 mmol) was oxidized as described for **7** to give the ketone as a colorless oil (88 mg, 99%). $[\alpha]_D^{20}$ +84° ($c=0.4$). IR ν_{max} cm^{-1}: 1720. ^{1}H-NMR δ: 0.80 (3H, d, $J=7.0$ Hz), 0.83 (3H, d, $J=7.0$ Hz), 0.86 (3H, t, $J=6.5$ Hz), 1.04 (3H, t, $J=7.5$ Hz), 1.04 (3H, d, $J=6.5$ Hz), 1.11 (3H, d, $J=6.5$ Hz), 1.17—1.93 (6H, m), 2.33—2.68 (3H, m), 3.70 (1H, septet, $J=6.5$ Hz), 3.72 (1H, d, $J=13.0$ Hz), 4.60 (1H, d, $J=3.5$ Hz). MS *m/z* (relative intensity): 270 (M^+, 0.8), 228 (1.2), 210 (11.1), 100 (66), 57 (100). Exact MS *m/z* Calcd for $C_{16}H_{30}O_3$ (M^+): 270.2197. Found: 270.2170.

A toluene solution (2 ml) of the ketone (35 mg, 0.129 mmol) was added to a stirred toluene solution (2 ml) of Red-al (185 μl) at −70 °C under argon. After 30 min, the reaction mixture was allowed to warm to 0 °C during 1 h. The excess Red-al was decomposed with MeOH, and work-up gave **26** as a colorless oil (36 mg, 100%). $[\alpha]_D^{16}$ +131° ($c=1.28$). Acetate: ^{1}H-NMR δ: 0.81 (6H, d, $J=6.5$ Hz), 0.87 (3H, t, $J=7.5$ Hz), 0.97 (3H, t, $J=7.5$ Hz), 1.06 (3H, d, $J=6.5$ Hz), 1.17 (3H, d, $J=6.5$ Hz), 1.20—1.86 (9H, m), 2.04 (3H, s), 3.57 (1H, d, $J=10.5$ Hz), 3.83 (1H, septet, $J=6.5$ Hz), 4.61 (1H, d, $J=3.5$ Hz), 4.89 (1H, ddd, $J=8.5$, 5.0, 4.0 Hz). MS *m/z* (relative intensity): 314 (M^+, 0.2), 272 (1.7). 254 (2.5), 195 (44), 100 (100). Exact MS *m/z* $C_{18}H_{34}O_4$ (M^+): 314.2459. Found: 314.2461.

(2*R*,4*S*,5*S*,6*S*,7*S*)-6-Ethyl-7-(4-methoxybenzyloxy)-2,4-dimethylnonan-5-olide (27) Compound **26** (19 mg, 0.07 mmol) was treated with NaH (20 mg, 0.83 mmol) in DMF (0.3 ml) and then MPM chloride (117 μl, 0.83 mmol) at room temperature for 2 d as described for **25**. Work-up and chromatography on a silica gel column (*n*-hexane–EtOAc, 20:1) gave an MPM ether as a colorless oil (22 mg, 80%). $[\alpha]_D^{18}$ +81° ($c=0.88$). ^{1}H-NMR δ: 0.81 (3H, d, $J=7.0$ Hz), 0.83 (3H, d, $J=6.5$ Hz), 0.92 (3H, t, $J=7.5$ Hz), 0.99 (3H, t, $J=6.5$ Hz), 1.03 (3H, d, $J=6.5$ Hz), 1.08 (3H, d, $J=6.5$ Hz), 1.12—1.84 (9H, m), 3.29 (1H, ddd, $J=9.0$, 4.5, 3.0 Hz), 3.53 (1H, d, $J=10.0$ Hz), 3.80 (3H, s), 3.83 (1H, septet, $J=6.5$ Hz), 4.38 (1H, d, $J=11.0$ Hz), 4.51 (1H, d, $J=11.0$ Hz), 4.62 (1H, d, $J=3.5$ Hz), 6.86 (2H, d, $J=8.5$ Hz), 7.29 (2H, d, $J=8.5$ Hz). MS *m/z* (relative intensity): 332 (M^+-119, 1.2), 303 (0.8), 259 (1.0), 256 (1.3), 250 (1.1), 211 (3.7), 121 (100). Exact MS *m/z* Calcd for $C_{21}H_{32}O_3$ (M^+-119): 332.2353. Found: 332.2355.

A solution of the above oil (20 mg, 0.051 mmol) in THF (0.9 ml) and 1 N HCl (0.3 ml) was heated at 50 °C for 18 h. After neutralization with $NaHCO_3$, the mixture was evaporated *in vacuo*, and the residue was extracted with CH_2Cl_2. The extract was evaporated and the residue was chromatographed on a silica gel column (*n*-hexane–EtOAc, 4:1) to give a colorless oil (11.3 mg, 64%), which was treated with PCC(10 mg) and 3 Å molecular sieves (10 mg) in CH_2Cl_2 (0.5 ml) at room temperature for 2.5 h. Chromatography on a short silica gel column (*n*-hexane–EtOAc, 3:2) and silica gel TLC (benzene–Et_2O, 11:1) gave **27** as a colorless oil (10.8 mg, 96%). $[\alpha]_D^{17}$ +74° ($c=0.34$). IR ν_{max} cm^{-1}: 1730, 1620, 1590. ^{1}H-NMR δ: 0.92—1.02 (9H, m), 1.28 (3H, d, $J=7.5$ Hz), 1.15—2.02 (8H, m), 2.42—2.59 (1H, m), 3.58 (1H, ddd, $J=9.0$, 6.0, 3.0 Hz), 3.80 (3H, s), 4.35 (1H, d, $J=10.5$ Hz), 4.47 (1H, d, $J=11.0$ Hz), 4.57 (1H, d, $J=11.0$ Hz), 6.87 (2H, d, $J=9.0$ Hz), 7.27 (2H, d, $J=9.0$ Hz). MS *m/z* (relative intensity): 348 (M^+, 2.0), 264 (1.7), 212 (10.3), 121 (100). Exact MS *m/z* Calcd for $C_{21}H_{32}O_4$ (M^+): 348.2302. Found: 348.2314.

References and Notes

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17) There are several methods for the synthesis of 2,6-*trans*-tetrahydropyrans.[7,18] The method described here seems quite promising, because the stereoselective decarbonylation of some model compounds proceeded quite smoothly. These results will be reported elsewhere soon.

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21) The Wittig–Horner reaction with trimethyl 2-phosphonopropionate usually gives *Z*-α,β-unsaturated esters as main products. *Cf.* H. Nagaoka and Y. Kishi, *Tetrahedron*, **37**, 3873 (1981).

22) When **21** was carefully hydrogenated over Raney Ni, only the Bn group was removed,[15b,19] although some **21** remained unreacted, and, after isolation of the resulting alcohol, the remaining double bond was reduced with $Rh\text{-}Al_2O_3$ to give **22** with 57:1 stereoselectivity.

23) During a synthetic sequence protected hydroxy compounds are much easier to deal with than protected carbonyl compounds. Therefore, we planned to introduce the C11 carbonyl group by oxidation of the C11 hydroxy group in the final stage of the synthetic sequence involving the C10—C30 segments.[10] Since it was quite difficult to anticipate whether **25** or **27** would be more suitable, **25** and **27** were both synthesized.

24) The stereoselectivity fell to 4:1 when the solvent toluene was replaced by THF.