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Stereoselective Total Synthesis of Polyether Ionophore Antibiotics, Isolasalocid A and Lasalocid A. Part 2. The Total Synthesis *via* Stereoselective Construction of the B Rings by Chelation-Controlled Cyclization under Thermodynamic Conditions.[1]

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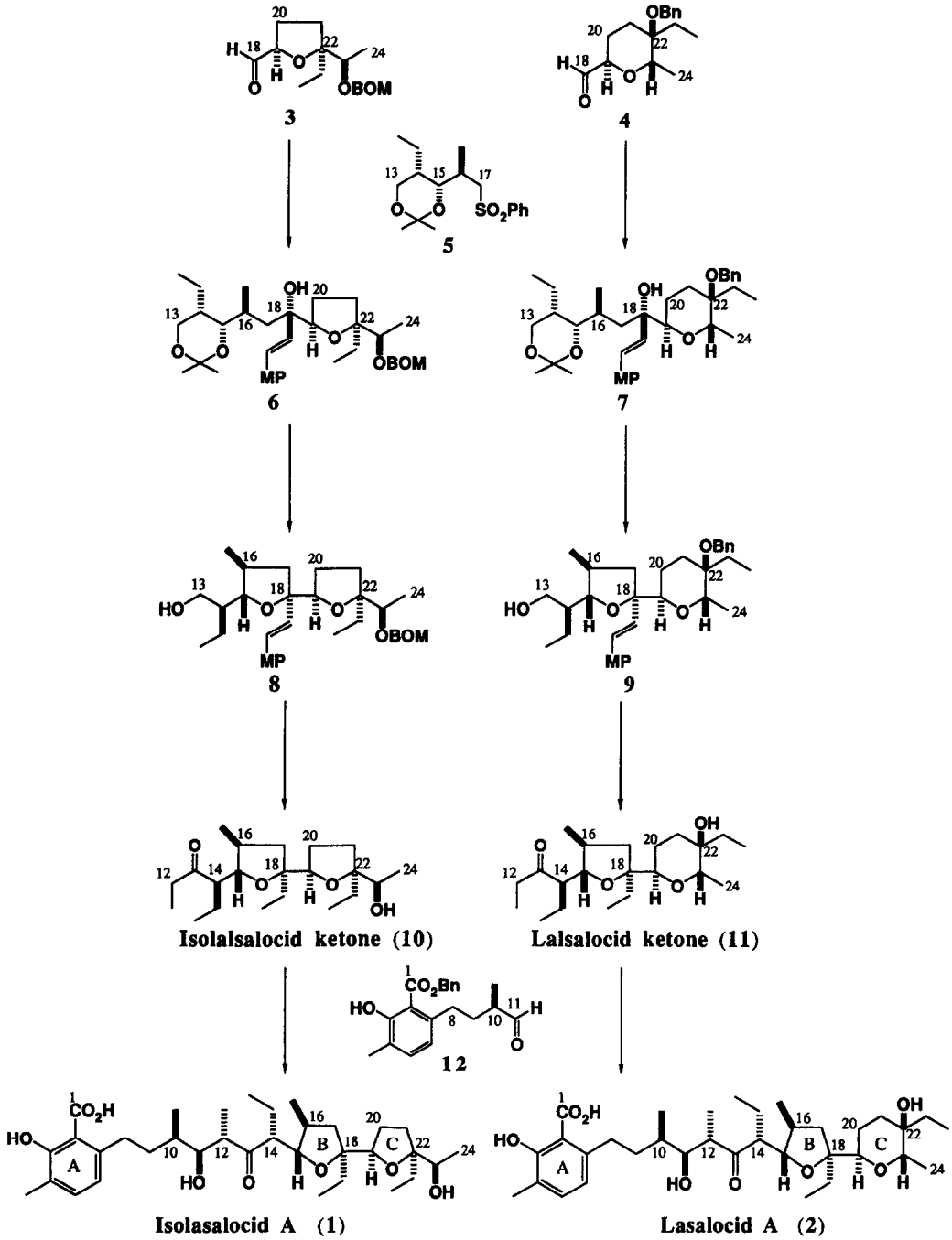
Abstract: Stereoselective total synthesis of isolasalocid A (**1**) and lasalocid A (**2**) was achieved *via* construction of the tetrahydrofuran rings by chelation-controlled cyclization of the corresponding *p*-methoxyphenyl substituted allyl alcohols (**6, 7**) under thermodynamic conditions.

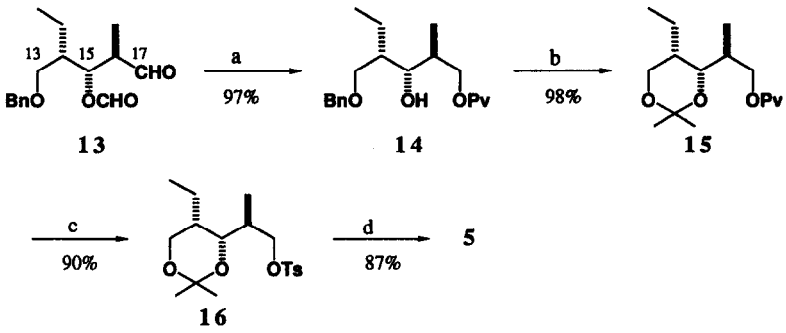
In the preceding paper,[1] we reported the synthesis of the C_{18}-C_{24} subunits (**3,4**) of isolasalocid A (**1**)[2] and lasalocid A (**2**)[3,4] *via* a stereoselective construction of the C rings as a successful application of a newly developed synthetic method of substituted tetrahydrofuran (THF) and tetrahydropyran (THP) rings by acid-catalyzed cyclization of *p*-methoxyphenyl (MP) substituted allyl alcohols.[5] This method was naturally applicable to the construction of the B rings. We report here a rather facile total synthesis of **1** and **2**, consisting of the construction of the B rings by chelation-controlled cyclization of the corresponding MP-allyl alcohols (**6,7**) under thermodynamic conditions, conversion of the C_{13}-C_{24} subunits (**8,9**) to isolasalocid ketone (**10**) and lasalocid ketone (**11**), and the final aldol condensation with the C_1-C_{11} aldehyde (**12**) leading to completion of the stereoselective total synthesis of isolasalocid A (**1**) and lasalocid A (**2**).[6]

Synthesis of the C_{13}-C_{24} MP-allyl alcohols (6,7)

The aldehyde (**13**)[7] readily derived from D-glucose was reduced with lithium aluminum hydride, and the resulting primary alcohol was selectively protected with a pivaloyl group to give **14**, which was hydrogenated over palladium charcoal, and then protection of the resulting diol as an acetonide gave **15**. The sulfone, C_{13}-C_{17} subunit (**5**), was readily obtained from **15** *via* the tosylate (**16**) and the iodide. The overall yield of **5** from **13** through eight conventional reactions was quite high (74%).

Among various conditions examined, the best result for the coupling between the C_{18}-C_{24} THF-aldehyde (**3**) and the C_{13}-C_{17} sulfone (**5**) was obtained as follows. When **3** was treated with an anion of **5** generated


3
4
5
6
7
8
9
Isolalsalocid ketone (10)
Lalsalocid ketone (11)
12
Isolasalocid A (1)
Lasalocid A (2)

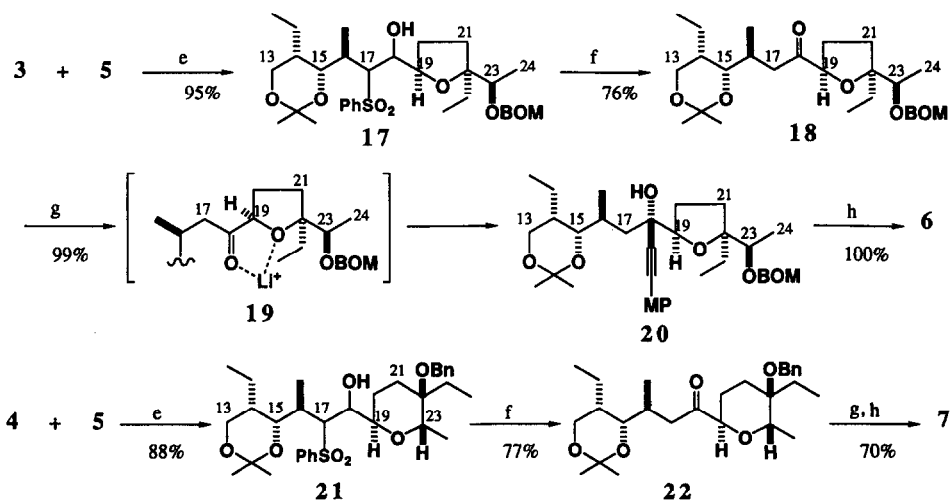


(a) 1) $LiAlH_4$, Et_2O, 0°~rt (99%); 2) PvCl, pyridine, 0°~rt (98%) (b) 1) H_2, 5%Pd/C, AcOEt, rt (100%); 2) CSA, $Me_2C(OMe)_2$, benzene, rt (98%) (c) 1) $LiAlH_4$, Et_2O, 0°~rt (96%); 2) TsCl, pyridine, 0°~rt (96%) (d) 1) NaI, acetone, reflux (94%); 2)$PhSO_2Na$, DMF, 60°C (93%)

Scheme 1

with *n*-butyllithium in *n*-hexane-ether (1:1) at -75°C,[8] the coupling proceeded quite smoothly to give a mixture of four diastereoisomeric β-hydroxysulfones (**17**) in excellent yield. Swern oxidation of **17** and desulfonization with aluminum amalgam[9] gave the ketone (**18**), which was treated with *p*-methoxyphenylethynyllithium at -78°C, and **20** was obtained as the single product in almost quantitative yield. This selective reaction presumably occurred through the attack of the ethynyl anion to the ketone chelated with a lithium cation (**19**) from the less-hindered side. Reduction of **20** with lithium aluminum hydride readily gave the C_{13}-C_{24} MP-*E*-allyl alcohol (**6**).

Similarly, the THP-aldehyde (**4**) was converted to the other C_{13}-C_{24} MP-*E*-allyl alcohol (**7**) *via* **21** and **22**.



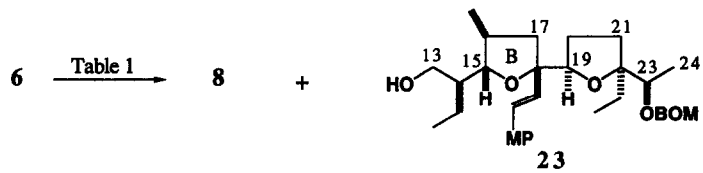
(e) ^nBuLi, Et_2O-^{n}hexane (1 : 1), **3** or **4** (f) 1) Swern Oxid.; 2) Al-Hg, THF, rt (g) MPC≡CLi, Et_2O, -78°~-30°C (h) $LiAlH_4$, THF, rt

Scheme 2

Cyclization of the MP-allyl alcohols (6,7) to the C_{13}-C_{24} subunits (8,9)

When the MP-allyl alcohol (**6**) was treated with *p*-toluenesulfonic acid (TsOH) in methanol at room temperature, the cyclization readily proceeded to give a 1:1.5 mixture of the desired THF (**8**) and the undesired THF (**23**)[10] (Table 1, entry 1). In dichloromethane and in tetrahydrofuran, the ratio of **8** to **23** was 1:3.5 and 1:5.6, respectively (entry 2,3). A little better yield of the mixture was obtained by the cyclization with *d*-camphorsulfonic acid (CSA) (entry 4). In benzene, the ratio was considerably shifted to **23** (1:10) (entry 5), and practically **23** was selectively obtained. These data indicate that there is almost no difference in thermodynamical stability between **8** and **23** though the main kinetic product is **23**.

Treatment of **6** with excess zinc bromide in dichloromethane caused a slight reversal of the product ratio (1.5:1) (entry 6). Quite interestingly, the ratio was gradually shifted to the desired THF (**8**), which was mainly obtained with a 7:1 selectivity after 7 hours.[11] Thus, it can be interpreted that **8** is a chelation-controlled cyclization product under thermodynamic conditions.

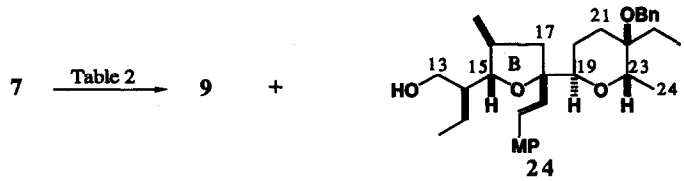


Scheme 3

Table 1. Acid Cyclization of the MP-allyl Alcohol (**6**)

entry	conditions	yield (%)	ratio **8** : **23**
1	TsOH, MeOH, rt, 1.5 h	63	1.0 : 1.5
2	TsOH, CH_2Cl_2, rt, 1.5 h	62	1.0 : 3.5
3	TsOH, THF, rt, 4.5 h	54	1.0 : 5.6
4	CSA, CH_2Cl_2, rt, 3 h	67	1.0 : 3.0
5	CSA, C_6H_6, rt, 3 h	76	1.0 : 10
6	$ZnBr_2$, CH_2Cl_2, rt, 2 h	77	1.5 : 1.0
7	$ZnBr_2$, CH_2Cl_2, rt, 7 h	58	7.0 : 1.0

Similarly, when the other MP-allyl alcohol (**7**) was first treated with CSA at room temperature in dichloromethane and in benzene, the cyclization of **7** proceeded smoothly and the undersired THF (**24**) was mainly obtained with 17:1 and 22:1 stereoselectivities, respectively (Table 2, entry 1,2). The selectivity of **24** decreased rather sharply with an increase in temperature (entry 3), and finally the ratio of **24** to the desired THF (**9**) was slightly reversed to 1:1.3 (entry 4). When **7** was treated with zinc bromide in dichloromethane even for a short time, the main product clearly changed to **9** with 3:1 stereoselectivity (entry 5). Under thermodynamic conditions, that is, on prolonged treatment with the bromide (entry 6) or at a higher temperature (entry 7), the selectivity was dramatically improved to 29-35:1.



Scheme 4

Table 2. Acid Cyclization of the MP-allyl Alcohol (7)

entry	conditions	yield (%)	ratio **9** : **24**
1	CSA, CH_2Cl_2, rt, 4 h	71	1.0 : 17
2	CSA, benzene, rt, 6 h	62	1.0 : 22
3	CSA, toluene, 50°C, 6 h	75	1.0 : 1.2
4	CSA, toluene, 90°C, 6 h	75	1.5 : 1.0
5	$ZnBr_2$, CH_2Cl_2, rt, 1 h	77	3.0 : 1.0
6	$ZnBr_2$, CH_2Cl_2, rt, 8 h	82	29 : 1.0
7	$ZnBr_2$, CH_2Cl_2, 40°C, 4 h	90	35 : 1.0

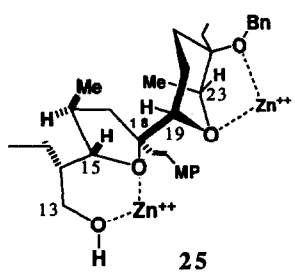
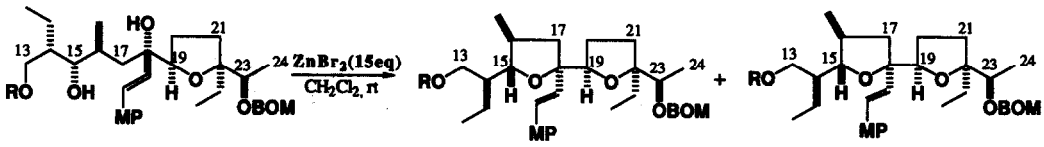


Table 3. Cyclization of **7** with Various Amounts of Zinc Bromide[1)]

entry	$ZnBr_2$ (eq)	yield (%)	ratio **9** : **24**	recovered **7** (%)
1	0.5	6.1	1.0 : 6.0	87
2	1.0	9.9	1.0 : 5.8	89
3	2.0	77	1.0 : 2.4	5.3
4	3.0	100	23.5 : 1.0	0

1) In dichloromethane at room temperature for 78 h
2) After 8 h, no **7** was detected on TLC.



26 : R = H (77%) **8** : R = H (6.7 : 1) **23** : R = H
27 : R = TBDPS (81%) **28** : R = TBDPS (1 : 1) **29** : R = TBDPS

Scheme 5

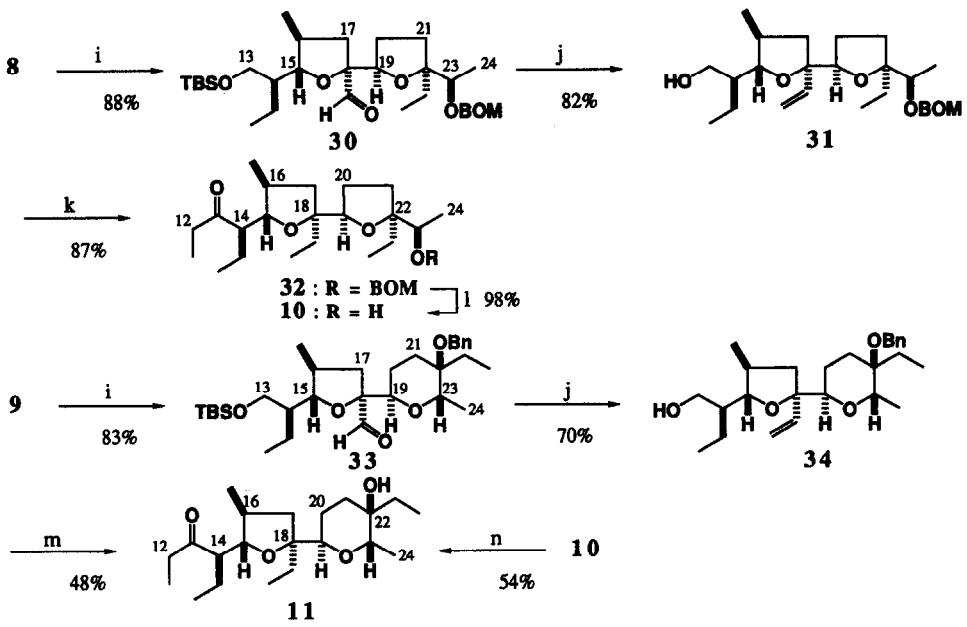
Thus, the stereoselective construction of the C_{13}-C_{24} subunits (**8**,**9**) was achieved. This THF ring cyclization with high stereoselectivity can be explained in terms of *a chelation-controlled cyclization under thermodynamic conditions via* the double chelation of zinc cations, leading to a thermodynamically favorable intermediate, e. g., **25**, on the basis of the following experimental results. 1) Relationship between efficiency of the cyclization and quantity of zinc bromide was first examined. Table 3 shows clearly that 3 molar equivalents of the bromide were required in order to obtain **9** selectively and efficiently.[12] 2) When a 1:19 mixture of **9** and **24** was treated with 0.5 molar equivalent of zinc bromide, the ratio of **9** to **24** in the mixture remained unchanged even after 6 days at room temperature. On the other hand, on treatment with 3 equivalents of the bromide, the ratio was completely reversed to 19:1 within 25 hours. 3) On treatment of the triol (**26**) with excess zinc bromide (15 equiv.) in dichloromethane at room temperature for 8 hours, the desired THF (**8**) was mainly obtained as a 6.7:1 mixture with **23** in 77% yield, whereas under the same conditions the silyl ether (**27**) gave a 1:1 mixture of **28** and **29** in 81% yield, because the C_{13}-silyloxy group was unable to chelate with zinc cation.

These data enabled us to demonstrate, for example, **25** as the most probable intermediate from **7** selectively to **9**, and in **25** two zinc cations are situated in positions apart from each other because of their ionic repulsion.

Total synthesis of isolasalocid A (1) and lasalocid A (2).

Isolasalocid ketone (**10**)[4a,13] and lasalocid ketone (**11**)[4,13] were derived from the corresponding C_{13}-C_{24} subunits, **8** and **9**, respectively, by a series of conventional reactions prior to completing the total synthesis of isolasalocid A (**1**) and lasalocid A (**2**). The primary alcohol of **8** was first protected with a *tert*-butyldimethylsilyl (TBS) group and the double bond was oxidized with osmium tetroxide and then lead tetraacetate to cleave to the aldehyde (**30**), which was converted to the olefin (**31**) *via* Wittig reaction and deprotection of the silyl group. Conversion of **31** to isolasalocid ketone (**10**)[4a,13] was as follows. The primary alcohol of **31** was oxidized with pyridinium chlorochromate (PCC) to an aldehyde, which was treated with ethylmagnesium bromide followed by oxidation with PCC again and then selective hydrogenation of the olefin over 10% palladium charcoal to give **32**. Finally rehydrogenation over palladium hydroxide gave **10** in excellent yield.

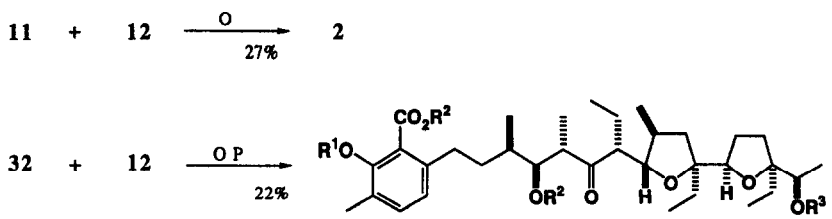
In the same manner, **9** was converted to lasalocid ketone (**11**)[4] without any difficulty *via* the aldehyde (**33**) and the olefin (**34**). Alternatively, **11** was readily obtained by the ring expansion reaction of **10** as reported by Kishi.[4a]



(i) 1) TBSCl, imidazole, CH_2Cl_2, rt; 2) OsO_4, NMO, acetone-H_2O (5 : 2), rt; 3) $Pb(OAc)_4$, benzene, rt (j) 1) $Ph_3P{=}CH_2$, THF; 2) $^nBu_4NF$, THF, rt (k) 1) PCC, 3A-MS, CH_2Cl_2, rt; 2) EtMgBr, THF, 0°C; 3) PCC, 3A-MS, CH_2Cl_2, rt; 4) H_2, 10%Pd/C AcOEt, rt (l) H_2, $Pd(OH)_2$, EtOH, rt (m) 1) H_2, $Pd(OH)_2$, AcOEt, rt; 2) PCC, 3A-MS, CH_2Cl_2, rt; 3) EtMgBr, THF, 0°C; 4) PCC 3A-MS, CH_2Cl_2, rt (n) 1) MsCl, pyridine, rt; 2) Ag_2CO_3, H_2O-acetone (1 : 4)

Scheme 6

Aldol condensation between **11** and the aldehyde (**12**) and subsequent hydrogenation in the manner described by Kishi[4a] gave lasalocid A (**2**) in 27% isolation yield. The physical data (mp, $[a]_D$, IR, 1H-NMR, MS, HR_MS) of this compound were identical with those of natural lasalocid A. Similarly, the ketone (**32**) was converted to its zinc enolate with lithium diisopropylamide (LDA) and zinc chloride, and then coupled with **12** to give a mixture of four diastereomeric aldol condensation products in 34% yield. The main product (22%; 41% based on the consumed **32**) was readily hydrogenated over palladium hydroxide, and isolasalocid A (**1**) was isolated in exellent yield.



(o) LDA, Et_2O, $ZnCl_2$, -78–0°C then **12**
(p) H_2, $Pd(OH)_2$, EtOH, rt

35 : R^1=Bn, R^2=H, R^3=BOM
36 : R^1=Bn, R^2=Ac, R^3=BOM
1 : R^1= R^2= R^3=H
37 : R^1=Bn, R^2=H, R^3=BOM

Scheme 7

Experimental

(2*S*,3*S*,4*S*)-4-Benzyloxymethyl-3-hydroxy-2-metyl-1-pivaloyloxyhexane (14)

A solution of **13** (0.90g, 3.23mmol) in anhydrous ether (5ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.25g, 6.6mmol) in ether under argon. After 5 min, a 10:1 mixture (11ml) of ether and MeOH was carefully added. H_2O (0.25ml), 15% aqueous NaOH (0.25ml), and H_2O (0.75ml) were successively added, and the mixture was filtered to remove insoluble inorganic salts, which were washed with ether. The aqueous layer of the filtrate was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 5:1-2:1) to give (2*S*,3*S*,4*S*)-4-benzyloxymethyl-2-methylhexane-1,3-diol as a colorless oil (0.81g, 99%). ^{1}H-NMR ($CDCl_3$) δ: 0.76 (d, 3H, *J*=7.0 Hz), 0.93 (t, 3H, *J*=7.0Hz), 1.44-1.74 (m, 4H), 1.78-2.16 (m, 2H), 3.61-3.83 (m, 5H), 4.50 (s, 2H), 7.33 (s, 5H). EI-MS *m/z* (%): 234 (M^+-18, 0.5), 193 (1.2), 143 (3.4), 108 (58), 107 (30), 91 (100). HR-MS Calcd for $C_{15}H_{22}O_2$ (M^+-18): 234.1619. Found: 234.1633.

Pivaloyl chloride (4.6ml) was added dropwise to a stirred solution of the above diol (5.8g, 23.0mmol) in pyridine (100ml) at 0°C, the stirring was continued overnight at room temperature, and then H_2O was added. After 2 hr, the reaction mixture was concentrated *in vacuo*, and ether and 2N HCl were added to the concentrate. The ether layer was separated, washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 16:1-6:1) to give **14** as a colorless oil (7.6g, 98%). $[\alpha]_D^{18}$ +3.7° (c=0.29, $CHCl_3$). IR (neat) ν (cm^{-1}): 3500, 1730. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (d, 3H, *J*=7.0Hz), 0.92 (t, 3H, *J*=7.5Hz), 1.20 (s, 9H), 1.42-1.56 (m, 2H), 1.60-1.68 (m, 1H), 1.92-2.03 (m, 1H), 3.11 (d, 1H, *J*=2.5Hz), 3.58 (dd, 1H, *J*= 3.0, 9.5Hz), 3.66 (d, 1H, *J*=9.0Hz), 3.71 (dd, 1H, *J*=4.0, 9.0Hz), 4.20 (d, 1H, *J*=5.0Hz), 4.48 (d, 1H, *J*=12.0Hz), 4.56 (d, 1H, *J*=12.0Hz), 7.32 (s, 5H). ^{13}C-NMR ($CDCl_3$) δ: 12.22 (q), 13.97 (q), 16.40 (t), 27.26 (q), 36.08 (d), 38.90 (s), 41.86 (d), 66.91 (t), 72.05 (t), 73.45 (t), 75.22 (d), 127.51 (d), 127.68 (d), 128.40 (d), 138.04 (s), 178.77 (s). EI-MS *m/z* (%): 337 (MH^+, 62), 319 (6.9), 223 (10), 211 (6.1), 154 (4.7), 127 (20), 109 (8.4), 91 (100), 85 (8.6), 57 (32). HR-MS Calcd for $C_{20}H_{33}O_4$ (MH^+): 337.2378. Found: 337.2395.

(2*S*)-2-[(4*S*,5*S*)-5-Ethyl-2,2-dimethyl-1,2-dioxan-4-yl]-1-pivaloyloxypropane (15)

A stirred solution of **14** (0.98g, 2.86mmol) in EtOAc (30ml) was hydrogenated over 5% Pd-C (0.98g) at room temperature for 6 hr. After the catalyst was removed by filtration, the filtrate was evaporated *in vacuo*, and the residue was chromatographed on a silica gel column to give (2*S*,3*S*,4*S*)-2-ethyl-4-methyl-5-pivaloyloxy-pentane-1,3-diol as a colorless oil (0.71g,100%). $[\alpha]_D^{18}$ -20° (c=1.14, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (d, 3H, *J*=7.0Hz), 0.98 (t, 3H, *J*=7.0Hz), 1.22 (s, 9H), 1.39-1.55 (m, 2H), 1.59-1.66 (m, 1H), 1.90-2.04 (m, 1H), 2.63 (brs, 1H), 3.37 (brs, 1H), 3.57 (d, 1H, *J*=10.0Hz), 3.76-3.87 (m, 2H), 4.01 (dd, 1H, *J*=4.0, 11.0Hz), 4.45 (dd, 1H, *J*=4.5, 11.0Hz). EI-MS *m/z* (%): 247 (MH^+, 4.3), 246 (M^+, 0.03), 173 (10), 145 (2.6), 103 (73), 85 (59), 57 (100). HR-MS Calcd for $C_{13}H_{26}O_4$ (M^+): 246.1831. Found: 246.1819.

A solution of the diol (1.7g, 6.91mmol), 2,2-dimethoxypropane (1.5ml) and a catalytic amount of CSA in benzene (10ml) was stirred at room temperature for 30 min. After addition of Et_3N (50ml), the mixture was concentrated *in vacuo*, and the residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 6:1) to give **15** as a colorless oil (1.93g, 98%). IR (neat) ν (cm^{-1}): 1730. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (d, 3H,

J=7.0Hz), 0.96 (t, 3H, *J*=7.5Hz), 1.21 (s, 9H), 1.36 (s, 3H), 1.39 (s, 3H), 1.26-1.47 (m, 2H), 3.75 (dd, 1H, *J*=2.5, 10.0Hz), 3.85-4.00 (m, 2H), 4.03 (d, 1H, *J*=10.5Hz), 4.13 (dd, 1H, *J*=3.5, 10.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 11.71 (q), 12.04 (q), 15.29 (t) 18.77 (q), 27.11 (q), 29.49 (q), 33.93 (d), 36.45 (d), 38.73 (s), 62.32 (t), 65.77 (t), 72.59 (d), 98.44 (s), 178.16 (s). EI-MS *m/z* (%): 271 (M^+-15, 23), 211 (4.0), 173 (20), 169 (9.0), 127 (16), 109 (60), 85 (57), 59 (73), 57 (100). HR-MS Calcd for $C_{15}H_{27}O_4$ (M^+-15): 271.1897. Found: 271.1902.

(2*S*)-2-[(4*S*,5*S*)-5-Ethyl-2,2-dimethyl-1,3-dioxan-4-yl]-1-tosyloxypropane (16)

To $LiAlH_4$ (0.18g, 4.74mmol) in anhydrous ether (7.0ml) was added slowly dropwise the pivaloate (**15**) (1.28g, 4.48mml) in anhydrous ether over 10 min under cooling with ice bath. After being stirred for 1.0 hr, excess reagent was quenched by addition of MeOH, H_2O (0.8ml), and 15% NaOH aqueous solution (0.2ml). After being stirred vigorously for 1.0 hr at room temperature, the insoluble solid was removed by suction filtration. After the filtrate was concentrared under reduced pressure, the resulting precipitate was purified on a silica gel column (*n*-hexane-EtOAc 6:1) to give (2*S*)-2-[(4*S*,5*S*)-5-ethyl-2,2-dimethyl-1,3-dioxan-4-yl]propan-1-ol as a colorless oil (0.87g, 96%). $[\alpha]_D^{24}$ +9.5° (c=2.04, $CHCl_3$). IR (neat) ν (cm^{-1}): 3450. ^{1}H-NMR ($CDCl_3$) δ: 0.76 (d, 3H, *J*=7.0Hz), 0.96 (t, 3H, *J*=7.5Hz), 1.16-1.25 (m, 1H), 1.38 (s, 3H), 1.38-1.48 (m, 1H), 1.49 (s, 3H), 1.69-1.83 (m, 1H), 1.90-2.04 (m, 1H), 3.08 (dd, 1H, *J*=3.0, 8.5Hz), 3.48-3.66 (m, 2H), 3.80-4.10 (m, 3H). EI-MS *m/z* (%): 187 (M^+-15, 19), 142 (2.2), 109 (20), 89 (20), 59 (100). HR-MS Calcd for $C_{10}H_{19}O_3$ (M^+-15): 187.1334. Found: 187.1329.

Tosyl chloride (2.1g, 11.0mmol) was added to a solution of the alcohol (1.15g, 5.69mmol) in pyridine (50ml) at 0°C, and the mixture was stirred at room temperature for 2 hr. After addition of H_2O, the reaction mixture was concentrated *in vacuo*, and then ether and 2N HCl were added. The aqueous layer was extracted with ether, and the combined organic layers were dried over $MgSO_4$, and evaporated. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 5:1) to give **16** as a colorless oil. (1.94g, 96%). $[\alpha]_D^{24}$ -8.4° (c=1.35, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (d, 3H, *J*=7.0Hz), 0.92 (t, 3H, *J*=7.5Hz), 1.06-1.28 (m, 2H), 1.26 (s, 3H), 1.30 (s, 3H), 1.58-2.14 (m, 2H), 2.45 (s, 3H), 3.72 (dd, 1H, *J*=2.0, 10.0Hz), 3.86 (br, 2H), 3.99 (dd, 1H, *J*=3.0, 9.0Hz), 4.14 (dd, 1H, *J*=5.0, 9.0Hz), 7.33 (m, 2H), 7.78 (m, 2H). EI-MS *m/z* (%): 341 (M^+-15, 0.4), 243 (13), 173 (26), 155 (24), 109 (100). HR-MS Calcd for $C_{17}H_{25}O_5S$ (M^+-15): 341.1422. Found: 341.1412.

(2*S*)-2-[(4*S*,5*S*)-5-Ethyl-2,2-dimethyl-1,3-dioxan-4-yl]propyl Phenyl Sulfone (5)

NaI (0.88g, 5.81mmol) was added to a stirred solution of **16** (1.10g, 3.09mmol) in acetone (10ml), and the mixture was heated at 60°C under reflux for 8 hr. After filtration of the reaction mixture, the filtrate was concentrated *in vacuo*, and the residue was purified on a silica gel column chromatography (*n*-hexane-EtOAc 10:1) to give an iodide as a colorless oil (0.91g, 94%). $[\alpha]_D^{17.5}$ -42° (c=1.74, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (d, 3H, *J*=6.5Hz), 0.94 (t, 3H, *J*=7.5Hz), 1.13-1.42 (m, 2 H), 1.36 (s, 3H), 1.47 (s, 3H), 1.60-1.99 (m, 2H), 3.31 (dd, 1H, *J*=2.5, 9.5Hz), 3.52 (dd, 1H, *J*=4.5, 10.0Hz), 3.61 (dd, 1H, *J*=2.4, 10.0Hz), 3.90 (br, 2H). EI-MS *m/z* (%): 313 (MH^+, 0.4), 297 (55), 237 (13), 195 (14), 109 (48), 59 (100), 43 (90) HR-MS Calcd for $C_{11}H_{22}O_2I$ (M^+-15): 313.0665. Found: 313.0674

$PhSO_2Na$ (0.84g, 5.06mmol) was added to a stirred solution of the iodide (0.91g, 2.92mmol) in DMF (10ml), and the mixture was heated at 60°C for 6 hr. After addition of ether and H_2O, the aqueous layer was extracted with ether, and the combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 10:1) to give **5**

as a colorless oil (0.88g, 93%). $[\alpha]_D^{24}$ -15° (c=1.02, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (t, 3H, *J*=7.0Hz), 1.07 (d, 3H, *J*=7.0Hz), 1.22 (s, 3H), 1.32 (s, 3H), 1.26-1.32 (m, 2H), 1.40-1.80 (m, 1H), 2.03-2.07 (m, 1H), 2.79 (dd, 1H, *J*=10.0, 14.0 Hz), 3.46 (dd, 1H, *J*=2.0, 4.5Hz), 3.58 (dd, 1H, *J*=2.0, 8.5Hz), 3.82 (d, 2H, *J*=2.0Hz), 7.45-7.67 (m, 3H), 7.86-7.96 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 11.59 (q), 14.62 (q), 15.09 (t), 18.90 (q), 29.41 (q), 30.71 (d), 36.10 (d), 58.42 (t), 62.05 (t), 74.54 (d), 98.62 (s), 127.68 (d), 129.01 (d), 133.29 (d), 140.14 (s). EI-MS *m/z* (%): 327 (MH^+, 8.2), 311 (39), 269 (1.6), 251 (9.9), 239 (3.0), 213 (16), 195 (3.9), 143 (51), 125 (23), 109 (100), 96 (13), 77 (46), 67 (16), 59 (65), 43 (36). HR-MS Calcd for $C_{17}H_{27}O_4S$ (MH^+): 327.1630. Found: 327.1638.

(1*RS*,2*RS*,3*S*)-2-{1-[(2*R*,5S)-((1*R*)-1-Benzyloxymethoxyethyl)-5-ethyltetrahydrofur-2-yl]-3-[(4*S*,5*S*)-5-ethyl-2,2-dimethyl-1,3-dioxan-4-yl]-1-hydroxy}butyl Phenyl Sulphone (17)

A 1.58M hexane solution of *n*-BuLi (0.87ml) was added dropwise to a stirred solution of **5** (482mg, 1.48mmol) in a mixture of *n*-hexane (3ml) and ether (3ml) at -75°C under argon. The suspended mixture was allowed to warm to room temperature, and after 15 min the pale yellow solution was cooled again at -75°C. A solution of **3** (115mg, 394μmol) in *n*-hexane (1ml) and ether (1ml) was added dropwise, and after 2 hr at -75 °C, the reaction was quenched with aqueous NH_4Cl. The reaction mixture was extracted with ether, and the extract was washed with brine, dried over Na_2SO_4, and evaporated to leave an oil, which was chromatographed on a silica gel column. Elution with CH_2Cl_2-benzene-EtOAc (30:30:1) gave the recovered **5** (353mg) and with *n*-hexane-EtOAc (8:1) afforded a four diastereoisomeric mixture of **17** as a colorless oil (231mg, 95%). IR (neat) ν (cm^{-1}): 3400. EI-MS *m/z* (%): 603 (M^+-15, 0.2), 589 (0.1), 495 (1.2), 453 (11), 293 (15), 235 (19), 143 (39), 91 (100). HR-MS Calcd for $C_{33}H_{47}O_8S$ (M^+-15): 603.2992. Found: 603.3019.

(3*S*)-1-{(2*R*,5*S*)-[(1*R*)-1-Benzyloxymethoxyethyl]-5-ethyltetrahydrofur-2-yl}-3-[(4*S*,5*S*)-5-ethyl-2,2-dimethyl-1,3-dioxan-4-yl]butan-1-one (18)

DMSO (0.28ml) in CH_2Cl_2 (0.5ml) was added dropwise to a stirred solution of oxalyl chloride (0.16ml, 1.83mmol) in CH_2Cl_2 (2ml) at -78°C under argon, and after 1 min, a solution of **17** (230mg, 372μmol) in CH_2Cl_2 (1ml) was added. After 1 hr, Et_3N (0.82ml) was added, and the stirring was continued for 3 hr. The reaction mixture was diluted with CH_2Cl_2 and H_2O, and 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 6:1) to give a two diastereoisomeric mixture of (2*RS*,3*S*,)-2-{1-[(2*R*,5*S*)-((1*R*)-1-benzyloxymethoxyethyl)-5-ethyltetrahydrofur-2-yl]-3-[(4*S*)-5-ethyl-2-tetrahydrofur-2-yl]-3-[(4*S*)-5-ethyl-2,2-dimethyl-1,3-dioxan-4-yl]-1-oxo}butyl phenyl sulfone as a colorless oil (209mg, 91%). Main product: IR (neat) ν (cm^{-1}): 1720. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (t, 3H, *J* = 7.0 Hz), 0.89 (t, 3H, *J* =7.0 Hz), 0.91 (d, 3H, *J* =7.0 Hz), 1.14~1.22 (m, 2H), 1.18 (d, 3H, *J*=6.0 Hz), 1.27 (s, 3H), 1.37 (s, 3H), 1.53 (q, 2H, *J*=7.0 Hz), 1.56~1.74 (m, 2H), 1.88~2.06 (m, 3H), 2.46 (ddq, 1H, *J*=2.0, 11.0, 7.0 Hz), 3.58 (dd, 1H, *J*=2.0, 11.0 Hz), 3.74 (q, 1H, *J*=6.0 Hz) 3.80 (brs, 2H), 4.39 (dd, 1H, *J*=7.0, 8.0 Hz), 4.57 (d, 1H, *J*=12.0 Hz), 4.66 (d, 1H, *J*=12.0 Hz), 4.75 (d, 1H, *J* =1.0 Hz), 4.78 (d, 1H, *J*=7.0 Hz), 4.85 (d, 1H, *J*=7.0 Hz),7.27~7.35 (m, 5H), 7.50 (dd, 2H, *J*=7.0, 8.0 Hz), 7.61 (t, 1H, *J*=7.0 Hz), 7.86 (d, 2H, *J*=8.0 Hz) EI-MS *m/z* (%): 601 (M^+-15, 0.8), 451 (2.8), 393 (2.0), 309 (9.1), 263 (9.5), 251 (14), 91 (100) HR-MS Calcd for $C_{33}H_{45}O_8S$ (M^+-15): 601.2835. Found: 601.2843.

Al-amalgam prepared from Al foil (150mg) and 2% $HgCl_2$ was added to a stirred solution of the ketosulfones (90.8mg, 147μmol) in 33% aqueous THF (3ml) at room temperature. After 3 hr, the reaction mixture was extracted with ether, and 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 8:1) to give **18** as a colorless oil (59.2mg, 84%). $[\alpha]_D^{15.5}$ +19° (c=0.36, $CHCl_3$). IR (neat) ν (cm^{-1}): 1705. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (d, 3H, *J*= 6.5Hz), 0.92 (t, 3H, *J*=7.5Hz), 0.93 (t, 3H, *J*=7.5Hz), 1.24 (d, 3H, *J*=6.0 Hz), 1.31 (s, 3H), 1.37 (s, 3H), 1.30-1.50 (m, 3H), 1.58 (q, 2H, *J*=7.0Hz), 1.60-1.80 (m, 2H), 1.82-1.98 (m, 1H), 2.00-2.18 (m, 2H), 2.20-2.30 (m, 2H), 2.85 (dd, 1H, *J*=8.0, 20.5Hz), 3.51 (dd, 1H, *J*= 2.0, 9.0Hz), 3.76 (q, 1H, *J*=6.0Hz), 3.82 (dd, 1H, *J*= 2.0, 12.0Hz), 3.88 (dd, 1H, *J*=2.0, 12.0 Hz), 4.30 (dd, 1H, *J*=7.0, 9.0Hz), 4.57 (d, 1H, *J*=12.0Hz), 4.67 (d, 1H, *J*=12.0Hz), 4.81 (d, 1H, *J*=7.0Hz), 4.84 (d, 1H, *J*=7.0Hz), 7.27-7.35 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ: 7.77 (q), 11.85 (q), 15.09 (q), 15.48 (t), 16.04 (q), 18.89 (q), 27.82 (t), 29.34 (t), 30.18 (q), 30.32 (d), 36.73 (t), 41.98 (t), 62.46 (t), 69.50 (t), 76.02 (d), 77.64 (d), 84.33 (d), 89.49 (s), 94.73 (t), 98.56 (s), 127.58 (d), 127.71 (d), 128.36 (d), 137.94 (s), 210.94 (s). EI-MS *m/z* (%): 476 (M^+, 0.8), 461 (0.3), 353 (1.2), 311 (10), 157 (12), 155 (17), 91 (100). HR-MS Calcd for $C_{28}H_{44}O_6$ (M^+): 476.3137. Found: 476.3132.

(3*R*,5*S*)-3-{(2*R*,5*S*)-[(1*R*)-1-Benzyloxymethoxyethyl]-5-ethyltetrahydrofur-2-yl}-5-[(4*S*,5*S*)-5-ethyl-2,2-dimethyl-1,3-dioxan-4-yl]-3-hydroxy-1-(4-methoxyphenyl)hex-1-yne (20)

A 1.58M hexane solution of *n*-BuLi (0.3ml) was added dropwise to a stirred solution of *p*-methoxyphenylacetylene (70mg, 0.53mmol) in anhydrous ether (3ml) at -78°C. After 30 min, a solution of **18** (80mg, 168μmol) in ether (2ml) was added, and the stirring was continued for 2 hr. The reaction was quenched with aqueous NH_4Cl, and the mixture was 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 10:1-5:1) to give **20** as a colorless oil (101mg, 99%). $[\alpha]_D^{18}$ +49° (c=1.64, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (t, 3H, *J*=7.5Hz), 0.95 (t, 3H, *J*=7.5Hz), 0.96 (t, 3H, *J*=7.0Hz), 1.20 (d, 3H, *J*=6.0Hz), 1.22-1.36 (m, 1H), 1.38-1.48 (m, 2H), 1.40 (s, 3H), 1.45 (s, 3H), 1.58 (q, 2H, *J*=7.5Hz), 1.66 (dd, 1H, *J*=6.0, 15.0Hz), 1.63-1.82 (m, 1H), 2.05-2.18 (m, 3H), 2.18-2.36 (m, 2H), 3.55 (dd, 1H, *J*=2.0, 10.0Hz), 3.77 (s, 3H), 3.78 (q, 1H, *J*=6.0Hz), 3.87-3.92 (m, 3H), 4.51 (d, 1H, *J*=12.0Hz), 4.59 (d, 1H, *J*= 2.0Hz), 4.73 (d, 1H, *J*=7.0Hz), 4.79 (d, 2H, *J*=7.0Hz), 5.14 (s, 1H), 6.75 (d, 2H, *J*= 6.0Hz), 7.29 (s, 5H), 7.35 (d, 2H, *J*=9.0Hz). ^{13}C-NMR ($CDCl_3$) δ: 7.90 (q), 11.89 (q), 15.48 (q), 15.48 (t), 18.20 (q), 19.09 (q), 26.79 (t), 27.82 (t), 29.47 (q), 30.65 (t), 31.19 (d), 37.22 (d), 45.94 (t), 55.23 (q), 62.42 (t), 69.45 (t), 73.62 (s), 77.09 (d), 78.20 (d), 84.70 (s), 85.83 (d), 88.23 (s), 89.61 (s), 94.60 (t), 99.20 (s), 113.78 (d), 115.66 (s), 127.48 (d), 127.76 (d), 128.32 (d), 133.07 (d), 138.24 (s), 159.27 (s). EI-MS *m/z* (%): 608 (M^+, 0.5), 590 (1.8), 487 (1.8), 485 (2.5), 429 (4.5), 385 (2.8), 367 (4.2), 345 (3.2), 311 (2.9), 287 (24), 155 (19), 91 (100). HR-MS Calcd for $C_{37}H_{52}O_7$ (M^+): 608.3712. Found: 608.3689.

(1*E*,3*R*,5*S*)-3-{(2*R*,5*S*)-[(1*R*)-1-Benzyloxymethoxyethyl]-5-ethyltetrahydrofur-2-yl}-5-[(4*S*,5*S*)-5-ethyl-2,2-dimethyl-1,3-dioxan-4-yl]-3-hydroxy-1-(4-methoxyphenyl)hex-1-ene (6)

$LiAlH_4$ (97.9mg) was added by portions to a stirred solution of **20** (102mg, 167μmol) in anhydrous THF (4ml) at 0°C. After the addition of $LiAlH_4$ was completed, a pH 7 buffer solution was added carefully to decompose excess $LiAlH_4$. The reaction mixture was stirred with ether for 3 hr, and the ether layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 5:1) to give **6** as a colorless oil (102mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.77 (d, 3H, *J*=7.0Hz), 0.88 (t, 3H, *J*=7.5Hz), 0.91 (t, 3H, *J*=7.5Hz), 1.21 (d, 3H, *J*=6.5Hz), 1.16-1.40 (m,

3H), 1.43 (s, 3H), 1.46 (s, 3H), 1.60 (q, 2H, *J*=7.5Hz), 1.46-1.67 (m, 2H), 1.83-1.95 (m, 5H), 3.49 (dd, 1H, *J*=2.0, 10.0Hz), 3.78 (s, 3H), 3.73-3.81 (m, 1H), 3.79 (q, 1H, *J*=6.5Hz), 3.84 (dd, 1H, *J*=2.0, 5.0Hz), 3.90 (dd, 1H, *J*=2.0, 12.0Hz), 4.51 (s, 1H), 4.56 (d, 1H, *J*=11.5Hz), 4.64 (d, 1H, *J*=11.5Hz), 4.82 (s, 2H), 6.15 (d, 1H, *J*= 16.0Hz), 6.66 (d, 1H, *J*=16.0Hz), 6.83 (d, 2H, *J*=9.0Hz), 7.21-7.33 (m, 5H), 7.33 (d, 2H, *J*= 9.0Hz). ^{13}C-NMR ($CDCl_3$) δ: 7.93 (q), 11.78 (q), 15.35 (q), 15.91 (q), 18.18 (q), 19.06 (q), 26.58 (t), 27.41 (t), 29.13 (d), 29.50 (q), 30.31 (t), 37.13 (d), 44.76 (t), 55.26 (q), 62.04 (t), 69.46 (t), 76.25 (s), 76.58 (d), 78.28 (d), 86.42 (d), 87.92 (s), 94.50 (t), 99.07 (s), 113.92 (d), 127.42 (d), 127.54 (d), 127.78 (d), 128.35 (d), 129.40 (d), 131.10 (d), 130.79 (s), 138.07 (s), 158.71 (s). EI-MS *m/z* (%): 592 (M^+-18, 23), 427 (4.7), 347 (30), 329 (14), 289 (60), 91 (100). HR-MS Calcd for $C_{37}H_{52}O_6$ (M^+-18): 592.3763. Found: 592.3758.

(1*RS*,2*RS*,3*S*)-2-{1-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-3-[(4*S*,5*S*)-5-ethyl-2,2-dimethyl-1,3-dioxan-4-yl]-1-hydroxy}butyl Phenyl Sulfone (21)

A solution of **5** (1.44g, 4.4mmol) in *n*-hexane (10ml) and ether (10ml) was treated with a 1.58M hexane solution of *n*-BuLi (2.7ml) and then a solution of **4** (0.42g, 1.6mmol) in ether (3ml) in a manner similar to the experiment for **17** to give a four deastereoisomeric mixture of **21** (853mg, 88%). EI-MS *m/z* (%): 573 (M^+-15, 0.6), 512 (0.6), 465 (3.8), 428 (3.6), 339 (7.5), 235 (16), 233 (18), 143 (29), 91 (100). HR-MS Calcd for $C_{32}H_{45}O_7S$ (M^+-15): 573.3763. Found: 573.2855.

(3*S*)-1-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-3-[(4*S*,5*S*)-5-ethyl-2,2-dimethyl-1,3-dioxan-4-yl]butan-1-one (22)

The mixture of **21** (211mg, 358μmol) was oxidized with oxalyl chloride (0.14ml) and DMSO (0.24ml) in CH_2Cl_2 as described for **18** to give a two diastereoisomeric mixture of (2*RS*,3*S*)-2-{1-[(2*R*,5*R*,6*S*)-5-benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]}-3-[(4*S*,5*S*)-5-ethyl-2,2-dimethyl-1,3-dioxan-4-yl]-1-oxo}-butyl phenyl sulfone as a colorless oil (210mg, 100%). IR (neat) ν (cm^{-1}): 1710. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (t, 3H, *J*=7.5Hz), 0.88 (t, 3H, *J*=7.5Hz), 0.89 (d, 3H, *J*=7.5Hz), 1.03 (s, 3H), 1.15 (s, 3H), 1.23 (d, 3H, *J*=7.0Hz), 1.00-1.76 (m, 7H), 1.80-1.88 (m, 1H), 1.92-2.02 (m, 1H), 2.17-2.26 (m, 1H), 3.40 (brd, 1H, *J*=11.5Hz), 3.55 (dd, 1H, *J*=2.0, 10.5Hz), 3.57 (dd, 1H, *J*= 1.5, 11.5Hz), 4.11 (q, 1H, *J*=7.0Hz), 4.07-4.14 (m, 1H), 4.24 (d, 1H, *J*=11.0Hz), 4.35 (d, 1H, *J*=11.0Hz), 5.34 (d, 1H, *J*=1.5Hz), 7.23-7.35 (m, 5H), 7.50-7.62 (m, 3H), 7.86-7.89 (m, 2H). EI-MS *m/z* (%): 571 (M^+-15, 0.2), 463 (0.6), 233 (17), 91 (100). HR-MS Calcd for $C_{32}H_{43}O_7S$ (M^+-15): 571.2729. Found: 573.2736.

The above ketosulfones (210mg, 358μmol) were treated with Al-amalgam prepared from Al foil (200mg) as described for **18** to give **22** as a colorless oil (124mg, 77%). $[\alpha]_D^{17}$ +2.9° (c= 0.83, $CHCl_3$). IR (neat) ν (cm^{-1}): 1700. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (d, 3H, *J*=6.0Hz), 0.92 (t, 3H, *J*=7.5Hz), 0.93 (t, 3H, *J*=7.5Hz), 1.26 (d, 3H, *J*=6.5Hz), 1.30 (s, 3H), 1.39 (s, 3H), 1.21-1.44 (m, 2H), 1.46-1.71 (m, 6H), 1.87-1.91 (m, 2H), 2.17-2.38 (m, 1H), 2,36 (dd, 1H, *J*= 8.0, 17.0Hz), 2.83 (dd, 1H, *J*=4.0, 17.0Hz), 3.52 (dd, 1H, *J*=2.5, 9.5Hz), 3.84 (dd, 1H, *J*=2.0, 12.5Hz), 3.90 (dd, 1H, *J*=2.0, 13.0Hz), 4.06 (q, 1H, *J*=6.5Hz), 4.03-4.08 (m, 1H), 4.33 (d, 1H, *J*=11.0Hz), 4.37 (d, 1H, *J*= 11.0Hz), 7.25-7.40 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ: 6.65 (q), 11.94 (q), 14.71 (q), 15.29 (q), 15.55 (t), 19.05 (q), 23.05 (t), 25.28 (t), 26.36 (t), 29.70 (q), 30.25 (d), 36.84 (d), 41.83 (t), 62.57 (t), 62.82 (t), 73.39 (d), 75.49 (d), 76.17 (d), 77.23 (s), 948.64 (s), 127.21 (d), 127.41 (d), 128.27 (d), 139.38 (s), 211.64 (s). EI-MS *m/z* (%): 446 (M^+, 0.2), 431 (0.6), 323 (1.1), 253 (2.0), 233 (7.9), 155 (6.6), 141 (13), 91 (100). HR-MS Calcd for $C_{27}H_{42}O_5$ (M^+): 446.3032. Found: 446.3035.

(1*E*,3*R*,5*S*)-3-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl)-5-[(4*S*,5*S*)-5-ethyl-2,2-dimethyl-1,3-dioxan-4-yl]-3-hydroxy-1-(4-methoxyphenyl)hex-1-ene (7)

A 1.58M hexane solution of *n*-BuLi (0.56ml of 1.6M solution in *n*-hexane, 0.90mmol) was added dropwise to a stirred solution of *p*-methoxyphenylacetylene (120mg, 0.90mmol) in freshly distilled ether (3ml) at -78°C. After 30 min, a solution of ketone (**22**) (124mg, 278μmol) in ether (3.0ml) was added, and the stirring was continued for 2 hr. The reaction was quenched with saturated NH_4Cl aqueous solution, and the mixture was 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 10:1-5:1) **20** to give (3*R*,5*S*)-3-[(2*R*,5*R*,6*S*)-5-benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl)]-5-[(4*S*,5*S*)-5-ethyl-2,2-dimethyl-1,3-dioxan-4-yl]-3-hydroxy-1-(4-methoxyphenyl)hex-1-yne as a colorless oil (115.5mg, 72%). $[\alpha]_D^{26}$ +35° (c= 2.10, $CHCl_3$). IR (neat) ν (cm^{-1}): 3330, 2200. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (t, 3H, *J*=7.5Hz), 0.95 (t, 3H, *J*=7.5Hz), 0.98 (d, 3H, *J*=7.0Hz), 1.27 (d, 3H, *J*=7.0Hz), 1.28-1.47 (m, 2H), 1.42 (s, 3H), 1.47 (s, 3H), 1.49-1.60 (m, 4H), 1.70-1.82 (m, 1H), 1.84 (d, 1H, *J*=13.5Hz), 1.97-2.06 (m, 1H), 2.09-2.15 (m, 1H), 2.21 (dd, 1H, *J*=2.0, 14.5Hz), 2.30-2.40 (m, 1H), 3.42 (dd, 1H, *J*=2.0, 11.0Hz), 3.57 (dd, 1H, *J*= 2.0, 12.0Hz), 3.78 (s, 3H), 3.87 (dd, 1H, *J*=2.0, 12.0Hz), 3.93 (dd, 1H, *J*= 2.0, 12.0Hz), 4.20 (q, 1H, *J*= 6.5Hz), 4.36 (d, 1H, *J*=11.0Hz), 4.45 (d, 1H, *J*=11.0Hz), 5.17 (s, 1H), 6.69 (d, 2H, *J*=9.0Hz), 7.10-7.16 (m, 3H), 7.24 (d, 2H, *J*=8.5Hz), 7.35-7.38 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 11.91 (q), 15.18 (q), 15.51 (t), 18.20 (q), 19.12 (q), 21.80 (t), 26.25 (t), 26.75 (t), 29.47 (d), 31.04 (q), 37.28 (q), 45.01 (t), 55.23 (d), 62.46 (t), 62.60 (t), 72.96 (d), 73.23 (d), 75.22 (d), 75.68 (s), 78.40 (d), 85.14 (s), 89.13 (s), 99.19 (s), 113.59 (d), 115.79 (s), 126.78 (d), 127.48 (d), 128.12 (d), 133.34 (s), 139.55 (s), 159.16 (s). EI-MS *m/z* (%): 578 (M^+, 0.3), 563 (0.4), 561 (0.3), 560 (0.7), 455 (0.9), 454 (1.0), 414 (1.4), 287 (37), 159 (15), 155 (13), 113 (12), 91 (100). HR-MS Calcd for $C_{36}H_{50}O_6$ (M^+): 578.3607. Found: 578.3594.

$LiAlH_4$ (60.0mg, 0.159mmol) was added by portions to a stirred solution of the above acetylene (91.7mg, 159μmol) in freshly distilled tetrahydrofuran (4.0ml) at 0°C. After the addition of $LiAlH_4$ was completed, a pH 7 buffer solution was added carefully to decompose excess $LiAlH_4$. The reaction mixture was stirred with ether for 3 hr, and the ether layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 5:1) to give **6** as a colorless oil (88.9mg, 97%). $[\alpha]_D^{17}$ +75° (c= 0.61, $CHCl_3$). IR (neat) ν (cm^{-1}): 3350. ^{1}H-NMR ($CDCl_3$) δ: 0.78 (d, 3H, *J*=7.0Hz), 0.87 (t, 3H, *J*=7.5Hz), 0.88 (t, 3H, *J*=7.0Hz), 1.27 (d, 3H, *J*=7.0Hz), 1.20-1.74 (m, 9H), 1.45 (s, 3H), 1.48 (s, 3H), 1.77-1.92 (m, 2H), 2.07 (dd, 1H, *J*=2.0, 14.5Hz), 3.38 (dd, 1H, *J*=3.0, 11.0Hz), 3.51 (dd, 1H, *J*=2.0, 10.0Hz), 3.82 (s, 3H), 3.83 (dd, 1H, *J*=1.5, 12.5Hz), 3.90 (dd, 1H, *J*=1.5, 12.5Hz), 4.10 (q, 1H, *J*=6.0Hz), 4.24 (d, 1H, *J*=10.5Hz), 4.33 (d, 1H, *J*=10.5Hz), 4.53 (brs, 1H) 6.19 (d, 1H, *J*=16.0Hz), 6.66 (d, 1H, *J*=16.0Hz), 6.81 (d, 2H, *J*=9.0Hz), 7.30-7.15 (m, 3H), 7.25-7.36 (m, 2H), 7.31 (d, 2H, *J*=9.0Hz). ^{13}C-NMR ($CDCl_3$) δ: 6.29 (q), 11.82 (q), 15.02 (q), 15.38 (t), 18.23 (q), 19.13 (q), 21.14 (t), 26.29 (t), 28.88 (t), 29.56 (q), 37.22 (q), 44.39 (t), 55.38 (d), 62.49 (t), 62.69 (t), 73.13 (d), 75.72 (d), 76.05 (d), 76.08 (d), 77.23 (s), 78.43 (d), 99.10 (s), 113.88 (d), 126.95 (s), 127.68 (d), 127.81 (d), 128.23 (d), 129.01 (d), 130.64 (d), 131.01 (s), 139.25 (s), 158.64 (s). EI-MS *m/z* (%): 562 (M^+-18, 3.3), 457 (1.5), 347 (47), 289 (83), 161 (42), 121 (30), 91 (100). HR-MS Calcd for $C_{36}H_{50}O_5$ (M^+-18): 562.3658. Found: 562.3665.

(2*S*)-2-{(2*S*,3*S*,5*R*)-5-[(2*R*,5*S*)-5-((1*R*)-Benzyloxymethoxyethyl)-5-ethyltetrahydrofur-2-yl]-5-[(1*E*)-2-(4-methoxyphenyl)ethenyl]-3-methyltetrahydrofur-2-yl}butan-1-ol (8)

$ZnBr_2$ (170mg) was added to a stirred solution of **6** (60.2mg, 108μmol) in CH_2Cl_2 (2ml) at room temperature. After 7 hr, Et_3N (0.1ml), and then CH_2Cl_2 and brine were added. The CH_2Cl_2 layer 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 4:1) to give **8** as a colorless oil (34.7mg, 58%). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (t, 3H, *J*=7.5Hz), 0.95 (d, 3H, *J*=6.0Hz), 0.97 (t, 3H, *J*=7.5Hz), 1.20 (d, 3H, *J*=6.5Hz), 1.40-1.75 (m, 7H), 1.78-1.98 (m, 3H), 2.03-2.17 (m, 2H), 2.84-2.94 (br, 1H), 3.71-3.79 (m, 4H), 3.79 (s, 3H), 3.97 (dd, 1H, *J*=6.0, 8.0Hz), 4.56 (d, 1H, *J*=11.5 Hz), 4.65 (d, 1H, *J*=11.5 Hz), 4.82 (s, 2H), 6.15 (d, 1H, *J*=16.0 Hz), 6.55 (d, 1H, *J*=16.0Hz), 6.82 (d, 2H, *J*=9.0Hz), 7.30 (d, 2H, *J*=9.0Hz), 7.25-7.37 (m, 5H). EI-MS *m/z* (%): 553 (MH^+) 523 (0.2), 445 (1.1), 415 (0.7), 409 (0.7), 387 (15), 369 (0.9) 315 (1.8), 289 (100), 161 (39), 91 (55). HR-MS Calcd for $C_{34}H_{49}O_6$ (MH^+): 553.3517. Found: 552.3532.

(2*S*)-2-{(2*S*,3*S*,5*S*)-5-[(2*R*,5*S*)-5-((1*R*)-1-Benzyloxymethoxyethyl)-5-ethyltetrahydro-fur-2-yl]-5-[(1*E*)-2-(4-methoxy-phenyl)eth-1-enyl]-3-methyltetrahydrofur-2-yl}butan-1-ol (23)

CSA (11.5mg) was added to a solution of **6** (8.0mg, 13.1μmol) at room temperature, and the mixture was sonicated for 30 sec and then stirred for 3 hr. Work-up as described above gave **23** as a colorless oil (5.5mg, 76%). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (t, 3H, *J*=7.5Hz), 0.97 (d, 3H, *J*=6.5Hz), 0.98 (t, 3H, *J*=7.5Hz), 1.17 (d, 3H, *J*=6.0Hz), 1.54 (q, 2H, *J*=7.5Hz), 1.40-1.59 (m, 2H), 1.61-1.87 (m, 4H), 1.90-2.09 (m, 2H), 2.12-2.23 (m, 1H), 2.34 (dd, 1H, *J*=9.0, 12.0Hz), 3.68-3.91 (m, 4H), 3.80 (s, 3H), 3.97 (dd, 1H, *J*=5.5, 7.5Hz), 4.54 (d, 1H, *J*=12.0Hz), 4.61 (d, 1H, *J*=12.0Hz), 4.72 (d, 1H, *J*=7.0Hz), 4.77 (d, 1H, *J*=7.0Hz), 6.13 (d, 1H, *J*=16.0Hz), 6.49 (d, 1H, *J*=16.0Hz), 6.83 (d, 2H, *J*=9.0Hz), 7.30 (d, 2H, *J*=9.0Hz), 7.25-7.34 (m, 5H). EI-MS *m/z* (%): 523 (M^+-29, 0.2), 445 (0.6), 419 (0.3), 381 (13), 289 (100), 161 (30), 91 (43). HR-MS Calcd for $C_{32}H_{43}O_6$ (M^+-29): 523.3045. Found: 523.3043.

(2*S*)-2-{(2*S*,3*S*,5*R*)-5-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-5-[(1*E*)-2-(4-methyoxy-phenyl)eth-1-enyl]-3-methyltetrahydrofur-2-yl}butan-1-ol (9)

A solution of **7** (63.8mg, 0.11mmol) in CH_2Cl_2 (2ml) was treated with $ZnBr_2$ (100mg, 446μmol) for 8 hr at room temperature. Work-up as described for **8** gave **9** as a colorless oil (47.5mg, 82%). $[\alpha]_D^{24.5}$ +37° (c= 1.71, $CHCl_3$). IR (neat) ν (cm^{-1}): 3350. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (t, 3H, *J*=7.5Hz), 0.96 (d, 3H, *J*=6.0Hz), 1.00 (t, 3H, *J*=7.5Hz), 1.28 (d, 3H, *J*=7.0Hz), 1.24-1.59 (m, 6H), 1.64-1.92 (m, 4H), 2.04-2.17 (m, 2H), 2.79-2.94 (br, 1H), 3.53 (dd, 1H, *J*=2.0, 11.5Hz), 3.71 (dd, 1H, *J*=2.0, 10.0Hz), 3.74-3.92 (m, 2H), 3.81 (s, 3H), 4.13 (q, 1H, *J*=7.0Hz), 4.24 (d, 1H, *J*=10.5Hz), 4.36 (d, 1H, *J*=10.5Hz), 6.21 (d, 1H, *J*=16.0Hz), 6.57 (d, 1H, *J*=16.0Hz), 6.79 (d, 2H, *J*=9.0Hz), 7.09-7.18 (m, 3H), 7.25 (d, 2H, *J*=9.0Hz), 7.26-7.30 (m, 2H). EI-MS *m/z* (%): 414 (M^+-108, 0.2), 289 (100), 161 (33), 91 (36). HR-MS Calcd for $C_{26}H_{38}O_4$ (M^+-108): 414.2770. Found: 414.2781.

(2*S*)-2-{(2*S*,3*S*,5*S*)-5-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-5-[(1*E*)-2-(4-methoxyphenyl)eth-1-enyl]-3-methyltetrahydrofur-2-yl}butan-1-ol (24)

7 (8.0mg, 13.1μmol) in benzene (500μl) was treated with CSA to give **24** as a colorless oil (62%). $[\alpha]_D^{23}$ +3.6° (c= 0.54, MeOH). IR (neat) ν (cm^{-1}): 3350. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (t, 3H, *J*=7.5Hz), 0.94 (t, 3H, *J*=7.5Hz), 0.97 (d, 3H, *J*=7.0Hz), 1.23 (d, 3H, *J*=6.5Hz), 1.30-2.05 (m, 11H), 2.17-2.24 (m, 1H), 2.42 (dd, 1H, *J*=9.0, 12.5 Hz), 3.55 (dd, 1H, *J*=2.0, 11.5Hz), 3.73 (dd, 1H, *J*=2.0, 2.5Hz), 3.76-3.82 (m, 2H), 3.81 (s, 3H), 4.16 (q, 1H, *J*=6.5Hz), 4.28 (d, 1H, *J*=11.0Hz), 4.43 (d, 1H, *J*=11.0Hz), 6.20 (d, 1H, *J*=16.0Hz), 6.52 (d, 1H, *J*=16.0Hz), 6.84 (d, 2H, *J*=7.0Hz), 7.21-7.41 (m, 5H), 7.35 (d, 2H, *J*=7.0Hz).

EI-MS *m/z* (%): 414 (M^+-108, 0.2), 289 (100), 161 (43), 91 (45). HR-MS Calcd for $C_{26}H_{38}O_4$ (M^+-108): 414.2770. Found: 414.2780.

(2*S*)-2-{(2*S*,3*S*,5*S*)-5-[(2*R*,5*S*)-5-((1*R*)-1-Benzyloxymethoxyethyl)-5-ethyltetrahydrofur-2-yl]-5-formyl-3-methyl-2-tetrahydrofuryl}butyl *tert*-Butyldimethylsilyl Ether (30)

Imidazole (42mg) and *tert*-butyldimethylsilyl (TBS) chloride (20mg, 132μmol) was added to a stirred solution of **8** (34.8mg, 63.0μmol) in CH_2Cl_2 (4ml) at 0°C. After 3 hr at room temperature, CH_2Cl_2 and H_2O were added, and the CH_2Cl_2 layer was separated, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 20:1) to give (2*S*)-2-{(2*R*,3*S*,5*R*)-5-[(2*R*,5*S*))-5-((1*R*)-1-benzyloxymethoxyethyl)-5-ethyltetrahydrofur-2-yl]-5-[(1*E*)-2-(4-methoxyphenyl)ethe-1-nyl]-3-methyltetrahydrofur-2-yl}butyl *tert*-butyldimethylsilyl ether as a colorless oil (41.0mg, 98%). ^{1}H-NMR ($CDCl_3$) δ: 0.04 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 0.91 (t, 3H, *J*=7.5Hz), 0.95 (t, 3H, *J*=7.5Hz), 0.97 (d, 3H, *J*=6.0Hz), 1.21 (d, 3H, *J*=6.5Hz), 1.33-1.72 (m, 7H), 1.78-1.94 (m, 3H), 1.99-2.15 (m, 2H), 3.61-3.74 (m, 3H), 3.76 (q, 1H, *J*=6.5Hz), 3.79 (s, 3H), 3.91 (dd, 1H, *J*=6.0, 7.5Hz), 4.56 (d, 1H, *J*=11.5Hz), 4.65 (d, 1H, *J*=11.5Hz), 4.82 (s, 2H), 6.17 (d, 1H, *J*=16.0Hz), 6.57 (d, 1H, *J*=16.0Hz), 6.81 (d, 2H, *J*=9.0Hz), 7.30 (d, 2H, *J*=9.0Hz), 7.27-7.36 (m, 5H). EI-MS *m/z* (%): 637 (M^+-29, 0.1), 609 (0.7), 558 (0.4), 501 (6.6), 403 (100), 271 (7.8), 161 (34), 91 (39). HR-MS Calcd for $C_{36}H_{53}O_6Si$ (M^+-29): 609.3610. Found: 609.3602.

OsO_4 (11mg) was added to a stirred solution of the silyl ether (66.2mg, 99.4μmol) and *N*-methylmorpholine oxide (NMO) (30.0mg, 222μmol) in acetone (2ml) and H_2O (1ml). After 6 hr, $Na_2S_2O_4$ (50mg), Celite (100mg), acetone (2ml) and H_2O (1ml) were added, and the stirring was continued overnight. After the insoluble materials were filtered off, the filtrate was adjusted to pH 7, and then concentrated *in vacuo*. Brine was added to the residue, and the mixture was extracted with ether. The extract was dried over Na_2SO_4, and evaporated to leave an oil, which was chromatographed on a silica gel column (CH_2Cl_2-MeOH 200:1) to give a diastereoisomeric mixture of (2*S*)-2-{(2*S*,3*S*,5*S*)-5-[(2*R*,5*S*)-5-((1*R*)-1-benzyloxymethoxy)ethyl)-5-ethyltetrahydrofur-2-yl]-5-[(1*RS*,2*RS*)-1,2-dihydroxy-2-(4-methoxyphenyl)ethyl]-3-methyltetrahydrofur-2-yl}butyl *tert*-butyldimethylsilyl ether as a colorless oil (66.0mg, 95%). ^{1}H-NMR ($CDCl_3$) δ: 0.02 (s, 6/5H), 0.04 (s, 9/5H), 0.06 (s, 6H), 0.88 (s, 18/5H), 0.90 (s, 27/5H), 0.92-0.98 (m, 9H), 1.23 (d, 6/5H, *J*=6.0Hz), 1.24 (d, 9/5H, *J*=6.0Hz), 1.19-1.42 (m, 2H), 1.48-1.64 (m, 6H), 1.84-2.29 (m, 4H), 2.96 (d, 3/5H, *J*=8.0Hz), 3.29 (d, 2/5H, *J*=8.5Hz), 3.37 (d, 3/5H, *J*=8.5Hz), 3.48 (brd, 3/5H, *J*=8.5Hz), 3.56-3.82 (m, 4H), 3.79 (s, 6/5H), 3.80 (s, 9/5H), 4.10 (d, 3/5H, *J*=2.0Hz), 4.17 (dd, 3/5H, *J*=5.0, 10.5Hz), 4.28 (dd, 2/5H, *J*=6.0, 9.0Hz), 4.57 (d, 3/5H, *J*= 11.5 Hz), 4.59 (d, 2/5H, *J*=11.5Hz), 4.67 (d, 2/5H, *J*=11.5 Hz), 4.68 (d, 2/5H, *J*=11.5Hz), 4.80 (d, 3/5H, *J*=7.0Hz), 4.84 (s, 4/5H), 4.85 (d, 3/5H, *J*=7.0Hz), 5.06 (br, 1H), 5.50 (d, 2/5H, *J*=3.0Hz), 6.86 (d, 4/5H, *J*=9.0Hz), 6.87 (d, 6/5H, *J*= 9.0 Hz), 7.28-7.35 (m, 7H). EI-MS *m/z* (%): 682 (M^+-18, 0.2), 625 (0.3), 564 (0.4), 546 (1.7), 533 (1.6), 517 (5.2), 455 (3.7), 403 (6.5), 301 (6.7), 121 (34), 91 (100). HR-MS Calcd for $C_{31}H_{53}O_5Si$ (M^+-167): 533.3660. Found: 533.3659.

$Pb(OAc)_4$ (23.4mg, 52.8μmol) was added to a stirred solution of the above diol (30.6mg, 43.7μmol) in anhydrous benzene (1.5ml) at room temperature under argon. After 10 min, the reaction mixture was directly chromatographed on a silica gel column (*n*-hexane-EtOAc 10:1) to give **30** as a colorless oil (23.0mg, 95%). IR (neat) ν (cm^{-1}): 1710. ^{1}H-NMR ($CDCl_3$) δ: 0.02 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 0.81-0.99 (m, 9H), 1.16 (d, 3H, *J*=6.5Hz), 1.25-1.65 (m, 7H), 1.78-2.04 (m, 4H), 2.40 (dd, 1H, *J*=6.5, 12.0Hz), 3.80-3.92 (m,

4H), 4.00-4.06 (m, 1H), 4.65 (d, 1H, *J*=11.5Hz), 4.69 (d, 1H, *J*=11.5Hz), 4.83 (s, 2H), 7.28-7.36 (m, 5H), 9.67 (s, 1H). *Anal* Calcd for $C_{32}H_{54}O_6Si$: C, 68.28; H, 9.67. Found: C, 68.35; H, 9.78.

(2*S*)-2-{(2*S*,3*S*,5*R*)-5-[(2*R*,5*S*)-5-((1*R*)-1-Benzyloxymethoxyethyl)-5-ethyltetrahydrofur-2-yl]-5-ethenyl-3-methyltetrahydrofur-2-yl}butan-1-ol (31)

A 1.6M hexane solution of *n*-BuLi (1.7ml, 2.72mmol) was added to a suspension of methyltriphenylphosphonium bromide (1.08g, 3.04mmol) in freshly distilled THF (10ml) at 0°C under argon. After 1 hr, a solution of **30** (226mg, 0.402mmol) in THF (3ml) was added dropwise, the resulting pale yellow solution was allowed to stirr overnight at room temperature, and then poured into cold saturated aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 15:1) to give a diastereomeric olefin (23mg, 12%) at C_{18} position and as the first fraction and an olefin as the second fraction (187mg, 83%). $[\alpha]_D^{24}$ +37° (c= 0.76, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.04 (s, 6H), 0.89 (s, 9H), 0.90 (t, 3H, *J*=6.0Hz), 0.93 (t, 3H, *J*=7.0Hz) 0.96 (d, 3H, *J*=6.0Hz), 1.19 (d, 3H, *J*=6.5Hz), 1.25-1.38 (m, 1H), 1.48-2.02 (m, 11H), 3.60 (dd, 1H, *J*=4.5, 7.5Hz), 3.62 (dd, 1H, *J*=2.5, 6.0Hz), 3.67 (dd, 1H, *J*=5.0, 9.5Hz), 3.72 (q, 1H, *J*=6.5Hz), 3.85 (dd, 1H, *J*=6.0, 9.5Hz), 4.58 (d, 1H, *J*=11.5Hz), 4.66 (d, 1H, *J*=11.5Hz), 4.81 (s, 2H), 5.07 (dd, 1H, *J*=2.0, 11.5Hz), 5.27 (dd, 1H, *J*=2.0, 17.0Hz), 5.89 (dd, 1H, *J*=11.5, 17.5Hz), 7.28-7.36 (m, 5H). EI-MS *m/z* (%): 560 (M^+, 0.2), 503 (2.3), 469 (1.8), 439 (2.7), 395 (16), 91 (100). HR-MS Calcd for $C_{33}H_{56}O_5Si$ (M^+): 560.3896. Found: 560.3923. Spectrum data of the diastereomer at C_{18} position: $[\alpha]_D^{24}$ +18° (c= 0.56, $CHCl_3$). ^{1}H NMR($CDCl_3$) δ: 0.04 (s, 6H), 0.88 (s, 9H), 0.89 (t, 3H, *J*= 7.5 Hz), 0.92 (t, 3H, *J*= 6.5 Hz), 0.96 (d, 3H, *J*= 6.5 Hz), 1.19 (d, 3H, *J*= 6.5 Hz), 1.32~1.44 (m, 1H), 1.45~2.22(m, 10H), 2.28(dd, 1H, *J*= 9.0, 12.5 Hz), 3,54 (dd, 1H, *J*= 4.0, 9.0 Hz), 3.61 (dd, 1H, *J*= 6.5, 10.0 Hz), 3.67 (dd, 1H, *J*= 5.0, 10.0 Hz), 3.73 (q, 1H, *J*= 6.5 Hz), 3.82 (dd, 1H, *J*= 6.5, 8.5 Hz), 4.59 (d, 1H, *J*= 12.0 Hz), 4.66 (d, 1H, *J*= 12.0 Hz), 4.80 (s, 2H), 4.99 (dd, 1H, *J*= 2.0, 10,5 Hz), 5.24 (dd, 1H, *J*= 2.0, 17.0 Hz), 5.91 (dd, 1H, *J*= 10.5, 17.5 Hz), 7.28~7.36 (m 5H). EI-MS m/z (relative intensity) 560 (M^+, 0.2), 531 (0.6), 503 (2.8), 4.69 (1.6), 439 (2.5), 395 (24), 91 (100). HR-MS Calcd for $C_{33}H_{56}O_5Si(M^+)$: 560.3896, Found: 560.3909

A solution of the above olefin (131mg, 234μmol) and 1.0M THF solution of *n*-Bu_4NF (0.35ml, 0.35mmol) in THF (0.65ml) was stirred for 12 hr at room temperature under argon. After evaporation of the solvent *in vacuo*, the residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 3:2) to give **31** as a colorless oil (103mg, 99%). $[\alpha]_D^{24}$ +45° (c= 0.76, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (t, 3H, *J*=7.5Hz), 0.93 (d, 3H, *J*=6.5Hz), 0.96 (t, 3H, *J*= 7.0Hz), 1.18 (d, 3H, *J*=6.5Hz), 1.25-2.06 (m, 11H), 2.34-2.46 (m, 1H), 2.85 (dd, 1H, *J*=3.0, 8.5Hz), 3.70 (dd, 1H, *J*=2.0, 9.5Hz), 3.76 (q, 1H, *J*=6.5Hz), 3.69-3.81 (m, 2H), 3.87 (dd, 1H, *J*=6.5, 8.5Hz), 4.59 (d, 1H, *J*=12.0Hz), 4.66 (d, 1H, *J*=12.0Hz), 4.79 (d, 1H, *J*=7.0Hz), 4.83 (d, 1H, *J*=7.0Hz), 5.09 (dd, 1H, *J*=2.0, 10.5Hz), 5.29 (dd, 1H, *J*= 2.0, 17.0Hz), 5.88 (1H, dd, *J*=10.5, 17.5Hz), 7.28-7.38 (m, 5H). EI-MS *m/z* (%): 355 (M^+-91, 0.8), 325 (1.7), 309 (1.6), 281 (16), 183 (7.4), 155 (7.9), 113 (16), 91 (100). HR-MS Calcd for $C_{20}H_{35}O_5$ (M^+-91): 355.2484. Found: 355.2505. *Anal* Calcd for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.60; H, 9.64.

(4*R*)-4-{(2*S*,3*S*,5*R*)-5-[(2*R*,5*S*)-5-((1*R*)-1-Benxyloxymethoxyethyl)-5-ethyltetrahydrofur-2-yl]-5-ethyl-3-methyltetrahydrofur-2-yl}hexan-3-one (32)

PCC (346mg, 1.60mmol) and powdered 3A molecular sieves (150mg) were added to a stirred solution of **31** (179mg, 0.401mmol) in CH_2Cl_2 (7ml) at room temperature. After 1.2 hr, the reaction mixture was poured

into ether (70ml), and the insoluble materials were filtered off. The filtrate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 6:1) to give (2*R*)-2-{(2*S*,3*S*,5*R*)-5-[(2*R*,5*S*)-5-((1*R*)-1-benzyloxymethoxyethyl)-5-ethyltetrahydrofur-2-yl]-5-ethenyl-3-methyltetrahydrofur-2-yl}butanal as a colorless oil (167mg, 94%). $[\alpha]_D^{24}$ +24° (c= 0.56, $CHCl_3$). IR (neat) ν (cm^{-1}): 3400, 1720. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (t, 3H, *J*=7.5Hz), 0.93 (t, 3H, *J*=7.5Hz), 0.96 (d, 3H, *J*=6.0Hz), 1.18 (d, 3H, *J*=6.5Hz), 1.51-2.06 (m, 11H), 2.33 (ddt, 1H, *J*=3.5, 6.0, 3.5Hz), 3.72 (q, 1H, *J*=6.5Hz), 3.78 (dd, 1H, *J*=5.0, 9.0Hz), 3.85, (dd, 1H, *J*=6.0, 8.5Hz), 4.58 (d, 1H, *J*=11.5Hz), 4.66 (d, 1H, *J*=11.5Hz), 4.81 (s, 2H), 5.10 (dd, 1H, *J*=2.0, 11.0Hz), 5.25 (dd, 1H, *J*=2.0, 17.0Hz), 5.89 (dd, 1H, *J*= 1.0, 17.0Hz), 7.28-7.36 (m, 5H), 9.71 (d, 1H, *J*=3.5Hz). EI-MS *m/z* (%): 415 (M^+-29, 0.2), 385 (0.4), 353 (1.7), 323 (5.5), 307 (3.2), 279 (99), 233 (13), 207 (19), 181 (25), 91 (100). HR-MS Calcd for $C_{25}H_{35}O_5$ (M^+-29): 415.2482. Found: 415.2458.

The above aldehyde (47mg, 0.106mmol) in THF (3.0ml) was added dropwise to a stirred solution of EtMgBr prepared from Mg (55mg, 2.26mmol) and EtBr (261mg, 2.4mmol) in THF (3ml) at -20°C under argon. After 30 min, the reaction mixture was poured into saturated aqueons NH_4Cl, and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 6:1) to give (3*RS*,4*S*)-4-{(2*S*,3*S*,5*R*)-5-[(2*R*,5*S*)-5-((1*R*)-1-benzyloxymethoxyethyl)-5-ethyltetrahydrofur-2-yl]-5-ethenyl-3-methyltetrahydrofur-2-yl}hexan-3-ol as a colorless oil (47mg, 93%). ^{1}H-NMR ($CDCl_3$) δ: 0.87-1.03 (m, 12H), 1.18 (d, 1H, *J*=6.5Hz), 3.72 (q, 1H, *J*=6.5Hz), 4,58 (d, 1H, *J*=12.0Hz), 4.64 (d, 1H, *J*=12.0Hz), 4.81 (s, 2H), 5.08 (dd, 1/2H, *J*= 2.0, 10.5Hz), 5.10 (dd, 1/2H, *J*= 2.0, 10.5Hz), 5.27 (dd, 1/2H, *J*= 2.0, 17.0Hz), 5.28, (dd, 1/2H, *J*= 2.0, 17.0Hz), 5.87 (dd, 1/2H, *J*= 10.5, 17.0Hz), 5.88 (dd, 1/2H, *J*= 10.5, 17.0Hz). EI-MS *m/z* (%): 474 (M^+, 0.5), 445 (0.3), 353 (10), 309 (86), 291 (17), 251 (17), 155 (78), 141 (83), 127 (99), 91 (100). HR-MS Calcd for $C_{29}H_{46}O_5$ (M^+): 474,3345. Found: 474.3338. *Anal* Calcd for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77. Found: C, 73.29; H, 9.96.

The above alcohol (159mg, 0.335mmol) was oxidized with PCC (289mg, 1.34mmol) in the presence of 3A molecular sieves (150mg) in CH_2Cl_2 (7ml) for 3 hr at room temperature. Work-up as described above gave (4*R*)-4-{(2*S*, 3*S*, 5*R*)-5-[(2*R*, 5*S*)-5-((1*R*)-1-benzyloxymethoxyethyl)-5-ethyltetrahydrofur-2-yl]-5-ethenyl-3-methyltetrahydrofur-2-yl}hexan-3-one as a colorless oil (159mg, 100%). $[\alpha]_D^{23.5}$ +11° (c= 1.44, $CHCl_3$). IR (neat) ν (cm^{-1}): 1710. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (t, 3H, *J*=7.5Hz), 0.88 (d, 3H, *J*=7.0Hz), 0.89 (t, 3H, *J*=7.0Hz), 1.02 (t, 3H, *J*=7.0Hz), 1.18 (d, 3H, *J*=6.0Hz), 1.50-2.02 (m, 11H), 2.48 (q, 1H, *J*=7.0Hz), 2.52 (q, 1H, *J*=7.5Hz), 2.58 (ddd, 1H, *J*=4.5, 6.5, 9.0Hz), 3.62 (dd, 1H, *J*=6.5, 9.0Hz), 3.72 (q, 1H, *J*=6.0Hz), 3.84 (dd, 1H, *J*= 6.0, 8.5Hz), 4.58 (d, 1H, *J*=11.5Hz), 4.66 (d, 1H, *J*=11.5Hz), 4.81 (s, 2H), 5.08 (dd, 1H, *J*= 2.0, 11.0Hz), 5.09 (dd, 1H, *J*=2.0, 17.0Hz), 5.87 (dd, 1H, *J*= 11.5, 17.5Hz), 7.28-7.36 (m, 5H). EI-MS *m/z* (%): 381 (M^+ -91, 1.1), 351 (2.2), 335 (0.8), 307 (23), 251 (9.5), 91 (100). HR-MS Calcd for $C_{22}H_{37}O_5$ (M^+-91): 381.2641. Found: 381.2624. *Anal* Calcd for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.60; H, 9.55.

A vigorously stirred solution of the above ethylketone (159mg, 0.336mmol) in EtOAc (5.0ml) was hydrogenated in the presence of 10% Pd-C (20mg) for 30 min. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column (*n*-hexane-EtOAc 7:1) to give **32** as a colorless oil (159mg, 100%). $[\alpha]_D^{23}$ +6.3° (c= 0.48, $CHCl_3$). IR (neat) ν (cm^{-1}): 1710. ^{1}H-NMR ($CDCl_3$) δ: 0.81 (t, 3H, *J*=7.5Hz), 0.84 (t, 3H, *J*=7.5Hz), 0.89 (t, 3H, *J*=7.5Hz), 0.90 (d,

3H, *J*=6.5Hz), 1.01 (t, 3H, *J*=7.5Hz), 1.20, (d, 3H, *J*=7.0Hz), 1.46-1.76 (m, 11H), 1.93-2.06 (m, 2H), 2.41 (dq, 1H, *J*=18.5, 7.5Hz), 2.61 (ddd, 1H, *J*=1.5, 5.0, 11.0Hz), 3.61 (dd, 1H, *J*=5.0, 9.5Hz), 3.74 (q, 1H, *J*=6.5Hz), 3.86 (dd, 1H, *J*=5.5, 9.5Hz), 4.58 (d, 1H, *J*=11.5Hz), 4.68 (d, 1H, *J*=11.5Hz), 4.81 (d, 1H, *J*=7.0Hz), 4.85 (d, 1H, *J*=7.0Hz) 7.28-7.36 (m, 5H). EI-MS *m/z* (%): 367 (M^+-107, 0.3), 337 (2.2), 323 (0.3), 319 (0.2), 309 (29), 253 (9.4), 235 (5.3), 211 (90), 155 (43), 91 (58), 57 (100). HR-MS Calcd for $C_{22}H_{39}O_4$ (M^+-107): 367.2848. Found: 367.2840.

(4*R*)-4-{(2*S*,3*S*,5*S*)-5-Ethyl-5-[(2*R*,5*S*)-5-ethyl-5-((1*R*)-1-hydroxyethyl)tetrahydrofur-2-yl]-3-methyltetrahydrofur-2-yl}hexan-3-one. (Isolasalocid Ketone) (10)

A vigorously stirred solution of **32** (30mg, 63.6μmol) in EtOAc (4.5ml) in the presence of $Pd(OH)_2$ (10mg) was hydrogenated for 30 min at room temperature. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo*, and the residue was chromatographed on a silica gel column (*n*-hexane-EtOAc 7:1) to give **10** as a colorless oil (22mg, 98%). $[\alpha]_D^{19}$ -30° (c= 0.32, $CHCl_3$). IR (neat) ν (cm^{-1}): 3400, 1710. ^{1}H-NMR ($CDCl_3$) δ: 0.81 (t, 3H, *J*=7.5Hz), 0.86 (t, 3H, *J*=7.5Hz), 0.90 (t, 3H, *J*=7.5Hz), 0.93 (d, 3H, *J*=7.0Hz), 1.01 (t, 3H, *J*=7.5Hz), 1.08 (d, 3H, *J*=6.0Hz), 1.14 -2.23 (m, 1H), 1.39 (dq, 1H, *J*=14.5, 7.5Hz), 1.46 (dq, 1H, *J*=15.0 7.5Hz), 1.34-1.48 (m, 1H), 1.48-1.62 (m, 2H), 1.65-1.80 (m, 2H), 1.80-1.99 (m, 1H), 1.85 (dd, 1H, *J*=3.5, 7.0Hz), 1.90 (dd, 1H, *J*=4.0, 7.0Hz), 2.11 (ddd, *J*= 3.5, 8.5, 12.0Hz), 2.12-2.25 (m, 1H), 2.39 (dq, 1H, *J*=21.5, 7.5Hz), 2.63 (dq, 1H, *J*= 21.5, 7.5Hz), 2.80 (ddd, 1H, *J*=3.5, 7.0, 11.0Hz), 3.57 (dd, 1H, *J*= 7.0, 9.5Hz), 3.77 (q, 1H, *J*=6.5Hz), 4.00 (dd, 1H, *J*=7.5, 9.0Hz), 4.07 (br, 1H). ^{13}C-NMR ($CDCl_3$) δ: 7.18 (q), 7.72 (q), 9.73 (q), 12.51 (q), 17.05 (q), 17.45 (q), 22.17 (t), 27.70 (t), 27.90 (t), 30.24 (t), 31.11 (t), 35.48 (d), 39.15 (t), 40.79 (t), 57.98 (d), 72.90 (d), 82.20 (d), 86.23 (s), 87.47 (d), 89.43 (s), 214.12 (s). EI-MS *m/z* (%): 325 (M^+-29, 0.4), 309 (12), 253 (5.1), 211 (69), 155 (38), 57 (100). HR-MS Calcd for $C_{19}H_{33}O_4$ (M^+-29): 325.2378. Found: 325.2383. *Anal* Calcd for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found: C, 71.36; H, 11.17.

(2*S*)-2-{(2*S*,3*S*,5*S*)-5-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-5-formyl-3-methyltetrahydrofur-2-yl]butyl *tert*-Butyldimethylsilyl Ether (33)

The alcohol (**9**) (47.5mg, 91μmol) in CH_2Cl_2 (1.0ml) was silylated with imidazole (71mg, 1.04mmol) and TBS chloride (31mg, 206μmol) as described for **30** to give (2*S*)-2-{(2*S*,3*S*,5*R*)-5-[(2*R*,5*R*,6*S*)-5-benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl)-5-[(1*E*)-2-(4-methoxyphenyl)ethenyl]-3-methyltetrahydrofur-2-yl}butyl *tert*-butyldimethylsilyl ether as a colorless oil (61.8mg, 100%). $[\alpha]_D^{24.5}$ +34° (c=2.12, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (s, 3H), 0.07 (s, 3H), 0.88 (t, 3H, *J*=7.5Hz), 0.89 (d, 3H, *J*=7.0Hz), 0.91 (s, 9H), 0.98 (t, 3H, *J*=7.5Hz), 1.29 (d, 3H, *J*=7.0Hz), 1.24-1.61 (m, 6H), 1.61-1.80 (m, 3H), 1.88 (brd, 1H, *J*=14.5Hz), 2.00-2.13 (m, 1H), 2.17 (dd, 1H, *J*=7.5, 11.5Hz), 3.53 (dd, 1H, *J*=2.0, 11.0Hz), 3.63-3.69 (m, 2H), 3.73 (dd, 1H, *J*=4.5, 10.0Hz), 3.81 (s, 3H), 4.13 (q, 1H, *J*=7.0Hz), 4.25 (d, 1H, *J*=10.5Hz), 4.37 (d, 1H, *J*=10.5Hz), 6.27 (d, 1H, *J*=16.0Hz), 6.60 (d, 1H, *J*=16.0Hz), 6.79 (d, 2H, *J*=9.0Hz), 7.05-7.18 (m, 3H), 7.25 (d, 2H, *J*=9.0Hz), 7.26-7.32 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: -5.47 (q), -5.31 (q), 6.31 (q), 13.02 (q), 14.97 (q), 16.30 (q), 18.31 (s), 19.54 (t), 22.12 (t), 25.95 (q), 26.13 (t), 26.32 (t), 34.80 (d), 45.48 (d), 46.23 (t), 55.35 (q), 62.62 (t), 62.89 (t), 73.01 (d), 75.13 (d), 75.79 (s), 84.22 (s), 85.44 (d), 113.88 (d), 126.98 (d), 127.55 (d), 127.70 (d), 127.76 (d), 128.25 (d), 130.66 (s), 131.24 (d), 139.29 (s), 158.70 (s). EI-MS *m/z* (%): 636 (M^+, 0.1), 579 (M^+-57, 0.6), 403 (100), 271 (8.5), 161 (36), 121 (15), 91 (37). HR-MS Calcd for $C_{35}H_{51}O_5Si$: (M^+): 579.3504. Found: 579.3502.

The silyl ether (20.8mg, 32.7μmol) was oxidized with OsO_4 (7mg) in the presence of NMO (27.6mg, 204μmol) in acetone (0.5ml)-H_2O (0.2ml) as described for **30** to give a mixture of diols (18.7mg, 85%), 18.3mg of which in benzene (1ml) was cleaved with $Pb(OAc)_4$ (51mg, 115μmol), and **33** was isolated as a colorless oil (14.2mg, 98%). $[\alpha]_D^{28.5}$ +40° (c= 1.19, $CHCl_3$). IR (neat) ν (cm^{-1}): 1720. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (s, 6H), 0.86 (t, 3H, *J*=7.5Hz), 0.88 (s, 9H), 0.92 (t, 3H, *J*=7.5Hz), 0.98 (d, 3H, *J*=6.5Hz), 1.20 (d, 3H, *J*=7.0Hz), 1.30-1.58 (m, 8H), 1.82-1.99 (m, 3H), 2.40 (dd, 1H, *J*=6.5, 12.5Hz), 3.63 (dd, 1H, *J*=6.0, 10.0Hz), 3.69 (dd, 1H, *J*=4.0, 5.0Hz), 3.66-3.74 (m, 1H), 3.75 (dd, 1H, *J*=2.0, 11.5Hz), 4.10 (q, 1H, *J*=7.0Hz), 4.30 (d, 1H, *J*=11.0Hz), 4.41 (d, 1H, *J*=11.0Hz), 7.24-7.29 (m, 5H), 9.71 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: -5.46 (q), -5.38 (q), 6.33 (q), 12.79 (q), 14.71 (q), 16.34 (q), 18.23 (s), 19.17 (t), 21.19 (t), 25.92 (q), 26.16 (t), 26.26 (t), 35.28 (d), 39.62 (t), 45.35 (d), 62.47 (t), 62.66 (t), 72.94 (d), 73.24 (d), 75.63 (s), 87.04 (d), 89.04 (s), 127.11 (d), 127.63 (d), 128.25 (d), 139.36 (s), 205.00 (d). EI-MS *m/z* (%): 503 (M^+-29, 2.4), 475 (0.7), 395 (1.6), 300 (8.3), 233 (4.3), 91 (100). HR-MS Calcd for $C_{30}H_{50}O_4Si$ (M^+-29): 503.3554. Found: 503.3542.

(2*S*)-2-{(2*S*,3*S*,5*R*)-5-[(2*R*,5*R*,6*S*)-5-Benzyloxy-5-ethyl-6-methyltetrahydropyran-2-yl]-5-ethenyl-3-methyltetrahydrofur-2-yl}butan-1-ol (34)

The aldehyde (**33**) (40.4mg, 75.9μmol) in freshly distilled tetrahydrofurn (2.0 ml) was added dropwise to a stirred solution of methylenetriphenylphosphorane in freshly distilled tetrahydrofuran (1.0ml), prepared from methyltriphenylphosphonium bromide (159mg, 446μmol) and *n*-BuLi (1.58M solution, 0.28ml) at 0°C under argon over 10 min. The resulting mixture was stirred for 15 hr at room temperature under argon, and then poured into aqueous NH_4Cl solution with ice. The aqueous mixture was extracted with ether. The extract was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residual precipitate was passed through a silica gel columun (*n*-hexane-EtOAc 20:1) to give an olefin as a colorless oil (28.3mg, 70%). $[\alpha]_D^{26}$ +48° (c= 1.07, $CHCl_3$). HR-MS Calcd for $C_{28}H_{45}O_4Si$ (M^+-57): 473.3085. Found: 473.3107.

The olefin (5.5mg) was treated with *n*-Bu_4NF (1M THF solution, 150μl) in THF (0.2ml) for 7 hr at room temperature. After removal of the solvent, the residue was chromatographed on a silica gel columun (*n*-hexane-EtOAc 7:1-5:1) to give **34** as a colorless oil (4.3mg, 100%). $[\alpha]_D^{26}$ +58° (c=1.87, $CHCl_3$). IR (neat) ν (cm^{-1}): 3450. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (t, 3H, *J*=7.5Hz), 0.95 (d, 3H, *J*=6.0Hz), 0.97 (t, 3H, *J*=7.5Hz), 1.26 (d, 3H, *J*=7.0Hz), 1.30-1.78 (m, 9H), 1.85-1.92 (m, 1H), 1.99-2.11 (m, 2H), 2.81-2.94 (br, 1H), 3.48 (dd, 1H, *J*=2.0, 22.5Hz), 3.68 (dd, 1H, *J*=2.0, 10.0Hz), 3.72-3.77 (m, 1H), 3.79-3.90 (m, 1H), 4.09 (q, 1H, *J*=7.0Hz), 4.29 (d, 1H, *J*=11.0Hz), 4.39 (d, 1H, *J*=10.5 Hz), 5.09 (dd, 1H, *J*=2.0, 11.0Hz), 5.26 (dd, 1H, *J*=2.0, 17.5Hz), 5.95 (dd, 1H, *J*=11.0, 17.5Hz), 7.24-7.35 (m, 3H), 7.39-7.42 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 6.32 (q), 12.51 (q), 15.00 (q), 15.13 (q), 16.82 (t), 21.94 (t), 26.09 (t), 26.35 (t), 33.99 (t), 42.37 (d), 43.48 (t), 62.52 (d), 64.89 (d), 72.90 (d), 74.38 (d), 75.79 (s), 85.32 (s), 90.13 (d), 113.37 (t), 127.08 (d), 127.64 (d), 128.17 (d), 139.46 (s), 140.43 (d). EI-MS *m/z* (%): 343 (M^+-108, 0.1), 325 (0.8), 309 (3.3), 233 (4.8), 183 (9.7), 141 (14), 113 (11), 91 (100). HR-MS Calcd for $C_{19}H_{33}O_3$ (M^+-108): 309.2429. Found: 309.2440.

(4*R*)-4-{(2*S*,3*S*,5*S*)-5-Ethyl-5-[(2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydro-pyran-2-yl]-3-methyltetrahydrofur-2-yl}hexan-3-one. (Lasalocid Ketone) (11)

A vigorously stirred solution of **34** (17.5mg, 42μmol) in EtOAc (1.0ml) was hydrogenated in the presence of $Pd(OH)_2$ (14mg). Work-up as usual gave (2*S*)-2-{(2*S*,3*S*,5*S*)-5-ethyl-5-[(2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydropyran-2-yl]-3-methyltetrahydrofur-2-yl}butan-1-ol as a colorless oil (11.5mg, 84%). $[\alpha]_D^{26}$

+13° (c= 1.04, $CHCl_3$). IR (neat) ν (cm^{-1}): 3570, 3460. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (t, 3H, *J*=7.5Hz), 0.91 (t, 3H, *J*=7.5Hz), 0.95 (d, 3H, *J*=6.5Hz), 0.96 (t, 3H, *J*=6.5Hz), 1.22 (d, 3H, *J*=6.5Hz), 1.34 (q, 1H, *J*=7.5Hz), 1.35 (q, 1H, *J*=7.5Hz), 1.39-1.66 (m, 10 H), 1.82 (dd, 1H, *J*=4.5, 12.5Hz), 2.00-2.18 (m, 1H), 2.50-2.70 (br, 1H), 2.89-2.99 (br, 1H), 3.53, (dt, 1H, *J*=2.5, 9.0Hz), 3.66 (dd, 1H, *J*=1.5, 10.5Hz), 3.71-3.82 (m, 2H), 3.78 (q, 1H, *J*=7.0Hz). ^{13}C-NMR ($CDCl_3$) δ: 6.42 (q), 7.98 (q), 12.47 (q), 14.24 (q), 15.88 (q), 16.76 (t), 21.50 (t), 28.77 (t), 29.34 (t), 30.44 (t), 35.04 (d), 40.10 (t), 42.27 (d), 64.85 (t), 71.00 (s), 72.94 (d), 76.99 (d), 84.99 (s), 89.79 (d). EI-MS *m/z* (%): 311 (M^+-17, 0.1), 310 (0.1), 299 (0.4), 255 (0.4), 237 (0.6), 185 (100), 167 (21), 149 (25), 113 (33). HR-MS Calcd for $C_{19}H_{35}O_3$ (M^+-17): 311.2586. Found: 311.2592.

The above alcohol (11.5mg, 35μmol) in CH_2Cl_2 (0.9ml) was oxidized with PCC (18.9mg, 88μmol) in the presence of 3A molecular sieves (20mg) as described for **32** to give (2*R*)-2-{(2*S*,3*S*,5*S*)-5-ethyl-5-[(2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydropyran-2-yl]-3-methyltetrahydrofur-2-yl}butanal as a colorless oil (9.0mg, 78%). IR (neat) ν (cm^{-1}): 3550, 1705. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (t, 3H, *J*=7.5Hz), 0.93 (t, 6H, *J*=7.5Hz), 0.97 (d, 3H, *J*=6.0Hz), 1.21 (d, 3H, *J*=7.0Hz), 1.34 (q, 1H, *J*=7.5Hz), 1.35 (q, 1H, *J*=7.5Hz), 1.47 (q, 1H, *J*=7.5Hz), 1.52 (q, 1H, *J*=7.5Hz), 1.52-1.67 (m, 6H), 1.78-1.93 (m, 1H), 1.88 (dd, 1H, *J*=8.0, 10.5Hz), 1.98-2.11 (m, 1H), 2.31 (ddt, 1H, *J*=3.0, 9.5, 4.0Hz), 2.52-2.72 (brs, 1H), 3.51 (dd, 1H, *J*=3.0, 9.5Hz), 3.77 (dd, 1H, *J*=4.0, 10.0Hz), 3.79 (q, 1H, *J*=7.0Hz), 9.74 (d, 1H, *J*=3.0Hz). ^{13}C-NMR ($CDCl_3$) δ: 6.42 (q), 8.05 (q), 12.58 (q), 14.20 (q), 16.24 (q), 17.35 (t), 21.35 (t), 28.67 (t), 29.33 (t), 30.44 (t), 36.54 (d), 40.11 (t), 56.48 (d), 70.98 (s), 72.97 (d), 77.03 (d), 84.75 (d), 85.09 (s), 205.16 (d). EI-MS *m/z* (%) 326 (M^+, 0.2), 309 (0.2), 308 (0.1), 297 (0.8), 183 (100) 113 (23), 111 (20), 109 (26). HR-MS Calcd for $C_{19}H_{34}O_4$ (M^+): 326.2457. Found: 326.2451.

To EtMgBr in freshly distilled tetrahydrofuran (1.0ml), prepared from Mg (50mg) and freshly distilled EtBr (0.2ml), was added slowly above aldehyde (5.6mg, 17μmol) in freshly distilled tetrahydrofuran (1.0ml) over 10 min at -20°C under argon. After being stirred for 40 min, the reaction mixture was poured into saturated NH_4Cl solution with ice, and extracted with ether. The extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel columun chromatography (*n*-hexzane-EtOAc 7:1) to give (3*RS*,4*S*)-4-{(2*S*,3*S*,5*S*)-5-ethyl-5-[(2*R*,5*R*,6*S*)-5-ethyl-5-hydroxy-6-methyltetrahydropyran-2-yl]-3-methyltetrahydrofur-2-yl]hexan-3-ol as a colorless oil (5.0mg, 82%). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (t, 3H, *J*=7.5Hz), 0.92 (d, 3H, *J*=6.0Hz), 0.92 (t, 3H, *J*=7.5Hz), 0.94 (t, 3H, *J*=7.5Hz), 0.95 (t, 3H, *J*=7.5Hz), 1.23 (d, 3H, *J*=7.0Hz), 1.30-1.44 (m, 4H), 1.41-1.52 (m, 4H), 1.55-1.68 (m, 6H), 1.75 (dd, 1H, *J*=7.0, 12.0Hz), 2.02-2.15 (m, 1H), 3.55 (dd, 1H, *J*=4.0, 8.5Hz), 3.66-3.74 (m, 1H), 3.87 (dd, 1H, *J*=2.0, 10.5Hz), 3.89 (q, 1H, *J*=7.0Hz). ^{13}C-NMR ($CDCl_3$) δ: 6.44 (q), 7.86 (q), 10.93 (q), 12.71 (q), 14.25 (q), 15.29 (q), 17.38 (t), 21.86 (t), 28.87 (t), 29.30 (t), 29.42 (t), 30.47 (t), 35.09 (d), 39.08 (t), 42.70 (d), 71.00 (s), 73.13 (d), 73.66 (d), 76.83 (d), 85.11 (d).

The alcohol (17.1mg, 48μmol) was oxidized with PCC and molecular sieves to give **11** as a colorless oil (14.9mg, 88%). $[\alpha]_D^{24}$ -20° (c= 1.02, $CHCl_3$). IR (neat) ν (cm^{-1}): 3540, 1700. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (t, 6H, *J*=7.5Hz), 0.91 (t, 3H, *J*=7.5Hz), 0.92 (d, 3H, *J*=6.5Hz), 1.03 (t, 3H, *J*=7.5Hz), 1.21 (d, 3H, *J*=7.0Hz), 1.35 (dq, 2H, *J*=5.5, 7.5Hz), 1.40-1.66 (m, 8H), 1.72-1.83 (m, 1H), 1.85 (dd, 1H, *J*=8.0, 12.5Hz), 1.92-2.06 (m, 1H), 2.45 (dq, 1H, *J*=18.5, 7.5Hz), 2.60 (dq, 1H, *J*=18.5, 7.5Hz), 2.56-2.63 (m, 1H), 3.50 (brd, 1H, *J*=9.0Hz), 3.57 (dd, 1H, *J*=5.0, 9.5Hz), 3.78 (q, 1H, *J*=7.0Hz). ^{13}C-NMR ($CDCl_3$) δ: 6.41 (q), 7.40 (q), 8.05 (q), 12.45 (q), 14.12 (q), 16.70 (q), 21.09 (t), 21.31 (t), 28.59 (t), 29.31 (t), 30.38

(t), 37.96 (d), 37.18 (t), 40.76 (t), 57.49 (d), 70.95 (s), 72.96 (d), 76.92 (d), 85.90 (s), 86.40 (d), 213.92 (s). EI-MS *m/z* (%): 337 (M^+-29, 0.2), 336 (0.1), 325 (0.9), 255 (0.7), 212 (14), 211 (85), 155 (40), 57 (100). HR-MS Calcd for $C_{19}H_{33}O_4$ (M^+-29): 325.2378. Found: 325.2371.

Isolasalocid A (1)

A solution of **32** (43mg, 90μmol) in freshly distilled ether (0.8ml) was added dropwise to a stirred solution of LDA (270μmol), prepared from freshly distilled diisopropylamine (38μl, 0.27mmol) and *n*-BuLi (169μl of 1.6M hexane solution, 0.27mmol), in freshly distilled ether (0.8ml) at -78°C under urgon. After 5min, $ZnCl_2$ (351μl of 0.77M solution in ether, 270μmol) was added dropwise, the resulting clear solution was stirred at 0°C for 20 min, and then a solution of **12** (44mg, 135μmol) in freshly distilled ether (0.7ml) was added. After 5 min at 0°C, the reaction was quenched with saturated aqueous NH_4Cl solution, 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 applied to a silica gel preparative TLC (*n*-hexane-EtOAc, 4:1) to give four isomeric aldol adducts as colorless oils [a (**35**): 16mg, 21.6%. b and c: 4.0mg, 5.4%. d: 5.0mg, 6.8%]. Benzyl 23-*O*-benzyloxymethylisolasalocid A (**35**): $[\alpha]_D^{17}$ -23° (c=0.44, $CHCl_3$). IR (neat) ν (cm^{-1}): 3400, 1710, 1660. ^{1}H-NMR ($CDCl_3$) δ: 0.69 (d, 3H, *J*=6.5Hz), 0.83 (t, 3H, *J*=7.5Hz), 0.86 (t, 3H, *J*=7.5Hz), 0.88 (t, 3H, *J*=7.5Hz), 0.96 (d, 3H, *J*=6.5Hz), 1.04 (d, 3H, *J*=7.0Hz), 1.19 (d, 3H, *J*=6.5Hz), 1.21-1.44 (m, 2H), 1.23-1.89 (m, 14H), 1.95-2.18 (m, 3H), 2.20 (s, 3H), 2.72-3.04 (m, 4H), 3.60 (dd, 1H, *J*=1.0, 9.0Hz), 3.64 (dd, 1H, *J*=4.0, 10.0Hz), 3.70 (q, 1H, *J*=6.5Hz), 3.87 (dd, 1H, *J*=5.0, 9.5Hz), 4.58 (d, 1H, *J*=11.5Hz), 4.66 (d, 1H, *J*=11.5Hz), 4.81 (s, 2H), 6.66 (d, 1H, *J*=7.5Hz), 7.15 (d, 1H, *J*=7.5Hz), 7.28-7.50 (m, 10H), 11.37 (s, 1H). FAB-MS *m/z* (%): 693 (M^+-107, 4.7), 663 (19), 635 (5.4), 613 (3.3), 537 (8.7), 365 (6.7), 337 (16), 319 (4.6), 309 (14), 275 (11), 255 (23), 237 (19), 211 (10), 91 (100), 57 (19). HR-MS Calcd for $C_{42}H_{61}O_8$ (M^+-107): 693.4370. Found: 693.4350. *Anal* Calcd for $C_{48}H_{66}O_9$: C, 73.25; H, 8.45. Found: C, 73.30; H, 8.74. Benzyl 23-*O*-benzyloxymethyl-2,10-*O*-diacetylisolasalocid A (**36**): ^{1}H-NMR ($CDCl_3$) δ: 0.81-0.95 (m, 3Hx5), 1.09 (d, 3H, *J*=7.5Hz), 1.19 (d, 3H, *J*=6.5Hz), 1.26-2.04 (m, 16H), 1.95 (s, 3H), 2.00 (s, 3H), 2.10 (s, 3H), 2.38-2.47 (m, 1H), 2.66-2.79 (m, 2H), 3.04 (dq, 1H, *J*=4.0, 7.0Hz), 3.69 (q, 1H, *J*=6.5Hz), 3.67 (dd, 1H, *J*=4.5, 9.0Hz), 3.86 (dd, 1H, *J*=5.0, 9.5Hz), 4.57 (d, 1H, *J*=11.5Hz), 4.67 (d, 1H, *J*=11.5Hz), 4.82 (s, 2H), 5.15 (dd, 1H, *J*=4.0, 7.0Hz), 5.33 (s, 2H), 7.00 (d, 1H, *J*=7.5Hz), 7.18 (d, 1H, *J*=7.5Hz), 7.27-7.54 (m, 10H).

A solution of **35** (9.0mg, 11.2μmol) in EtOH (1.0ml) was hydrogenated over Pd $(OH)_2$ (1mg) at room temperature for 15 min. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo*. The residue was chromatographed on a silica gel column (CH_2Cl_2-MeOH 13:1) to give **1** (6.2mg, 94%), mp 199-201° (CH_2Cl_2-*n*-hexane). $[\alpha]_D^{19}$ -41° (c=0.2, $CHCl_3$). IR (Nujol) ν (cm^{-1}): 3430, 1700, 1600. ^{1}H-NMR ($CDCl_3$) δ: 0.86-0.98 (m, 3Hx5), 1.02-1.13 (m, 3Hx2), 1.21-1.55 (m, 9H), 1.83-2.37 (m, 9H), 2.16 (s, 3H), 2.82-2.94 (m, 2H), 3.55-4.14 (m, 7H), 6.43 (d, 1H, *J*=7.5Hz), 6.98 (d, 1H, *J*=7.5Hz). 2,10-*O*-Diacetylisolasalocid A (**37**): ^{1}H-NMR ($CDCl_3$) δ: 0.84 (t, 3H, *J*=7.5Hz), 0.87 (t, 3H, *J*=7.5Hz), 0.92 (t, 3H, *J*=7.5Hz), 0.97 (d, 3H, *J*=7.0Hz), 1.01 (d, 3H, *J*=6.5Hz), 1.10 (d, 3H, *J*=7.5Hz), 1.13 (d, 3H, *J*=6.5Hz), 1.25-2.34 (m, 17H), 2.02 (s, 3H), 2.15 (s, 3H), 2.28 (s, 3H), 2.63-2.69 (m, 2H), 2.84-2.93 (m, 1H), 3.09 (dq, 1H, *J*=4.5, 8.0Hz), 3.64 (dd, 1H, *J*=4.0, 10.5 Hz), 3.92 (q, 1H, *J*=6.5Hz), 4.06 (dd, 1H, *J*=6.5, 8.5Hz), 5.29 (t, 1H, *J*=4.5Hz), 7.00 (d, 1H, *J*=7.5Hz), 7.19 (d, 1H, *J*=7.5Hz). FAB-MS *m/z* (%): 629 (M^++39, 100), 613 (M^++23, 10), 449 (10), 421 (9.3), 393 (21), 207 (16), 154 (18), 149 (15), 147 (17), 136

(19), 121 (18), 73 (11). HR-MS Calcd for $C_{34}H_{54}O_8K$ (M^++K): 629.3405. Found: 629.3425. Calcd for $C_{34}H_{54}O_8Na$ (M^++Na): 613.3703. Found: 613.3713.

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References and Notes

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10. Although separation of **8** and **23** on TLC was unsuccessful in this stage, the diastereomer at C_{18} position was removed by a silica gel column chromatography after four steps.
11. The selectivity is probably improved by further treatment with the bromide, but because the benzyloxymethyl (BOM) group was not completely stable under these conditions, the yield of **8** and **23** gradually fell, and therefore the reaction was stopped within 8 hours.
12. One mole of zinc bromide was probably consumed in order to dehydrate from **7**.
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