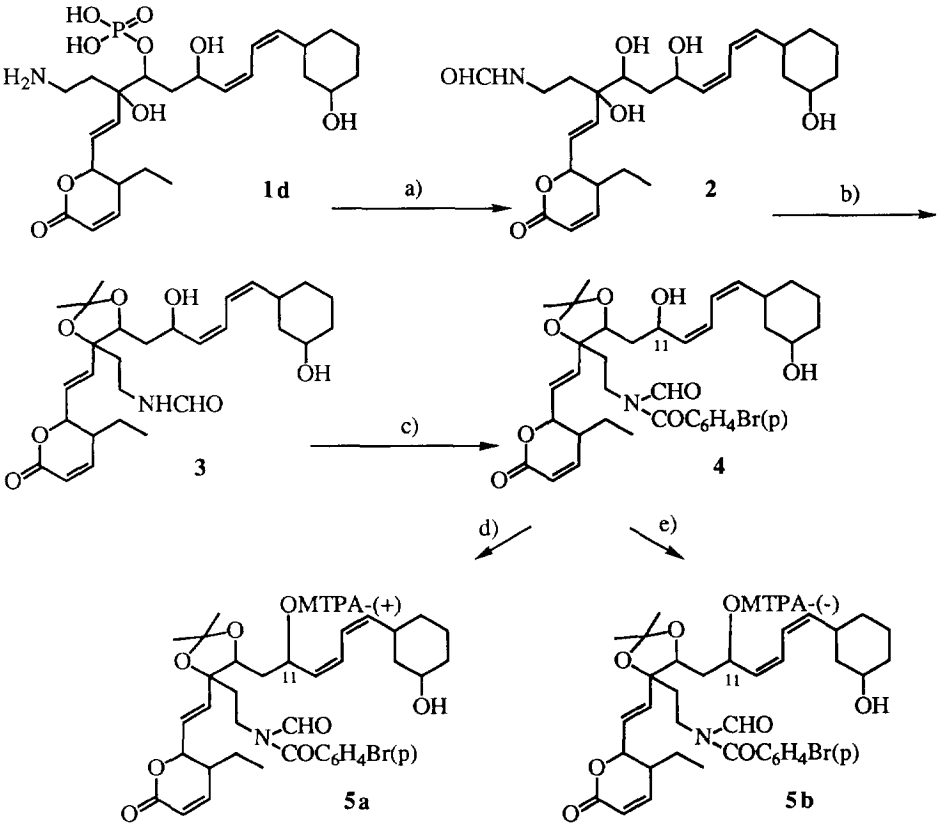

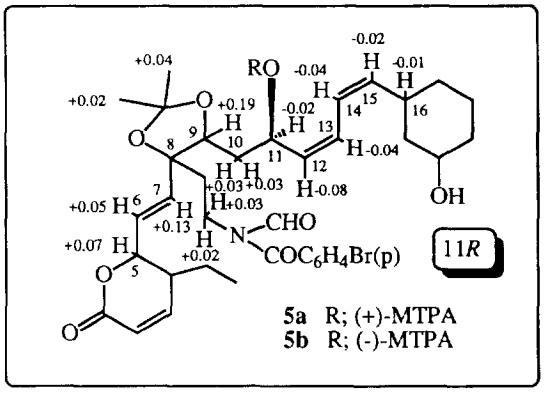

a) $HCONH_2$, phosphate buffer
b) CH_3COCH_3, *p*-TsOH
c) *p*-BrC_6H_4COCl, NEt_3
d) (+)-MTPACl, DMAP
e) (-)-MTPACl, DMAP

Fig.2. Preparation of **5a** and **5b**, and $\Delta\delta$ values (ppm) obtained from **5a** and **5b**

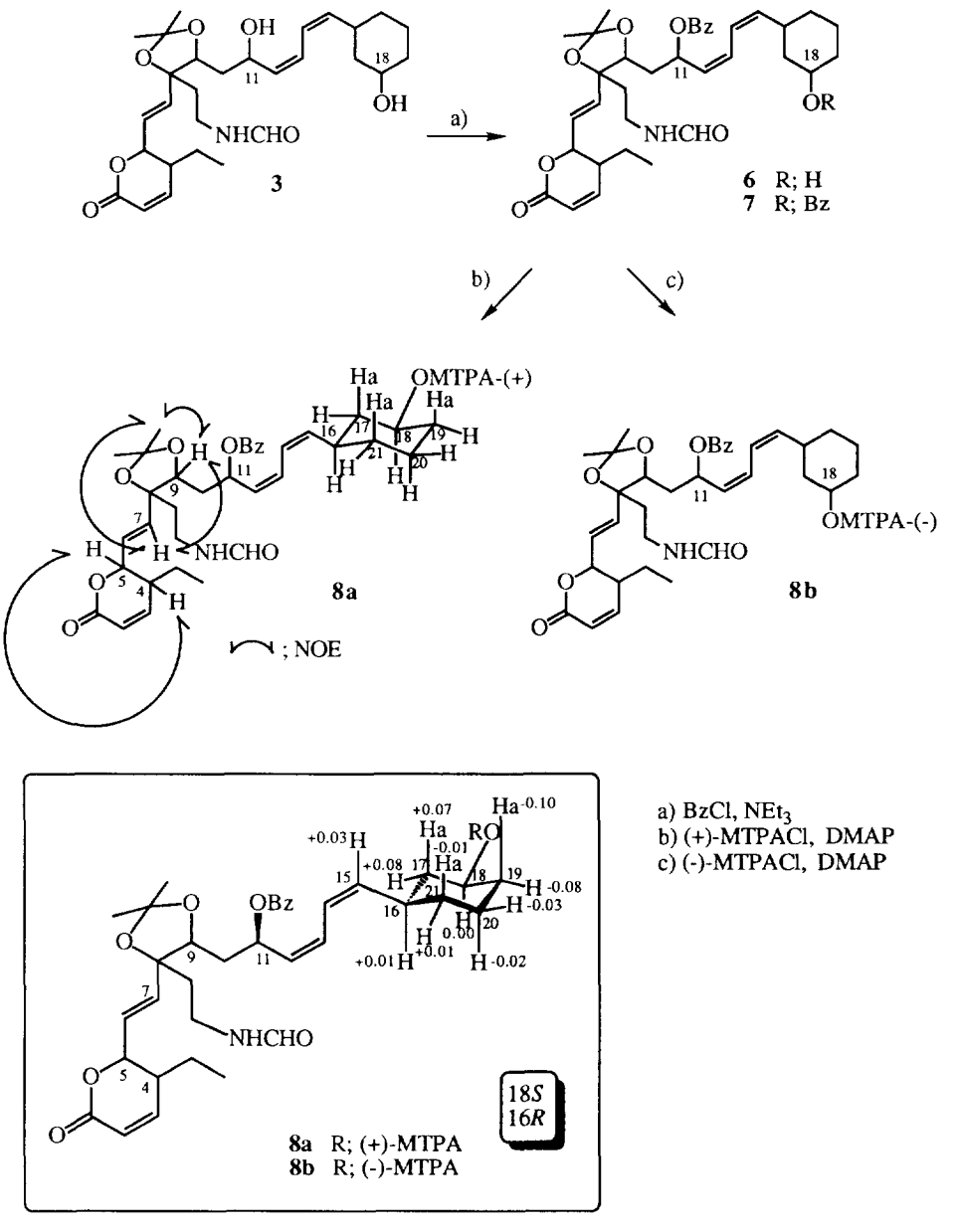

Fig.3. Preparation of **8a** and **8b**, and Δδ values obtained from **8a** and **8b**

Acid catalyzed hydrolysis of the acetonide function in **7** was not successful due to its inherent instability in acidic media. Therefore as an alternative route, regioselective acylation on the tetraol **2** was attempted. Thus **2** was treated with benzoyl chloride and DMAP to afford the main product as 11,18-O-dibenzoate **9** (y. 31%) along with 11-O-benzoate (y. 18%), 9, 11-O-dibenzoate (y. 15%), and 9,11,18-O-tribenzoate (y. 18%). Both (+)- and (-)-MTPA esters of the 9-hydroxy group of **9** were prepared to afford **10a** and **10b**, respectively. Analysis of proton NMR spectra of **10a** and **10b** showed that the Δδ values of H-5 - H-7 were negative and the Δδ values of H-10 - H-15 were positive. The Δδ values obtained from these MTPA esters are shown in Fig. 4. Analysis of the systematic arrangement of positive and negative Δδ's corroborated the *R* configuration at C-9. According to the relative stereochemistry mentioned above, the absolute configuration of C-8 must be *R*.

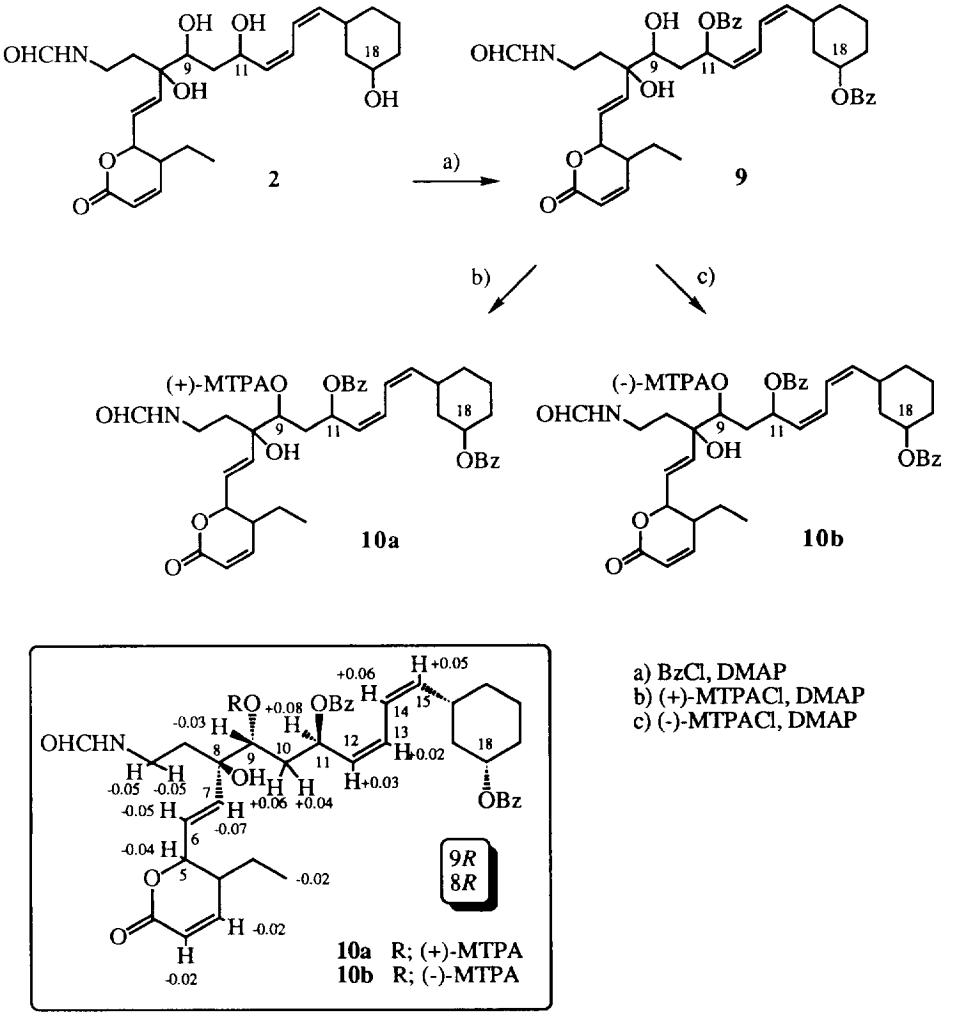

Fig.4. Preparation of **10a** and **10b**, and Δδ values obtained from **10a** and **10b**

Finally, to determine the absolute configuration of C-5, tetraol **2** was treated with sodium periodate to afford ketone **11**. Hydrogenation of **11** followed by alkaline hydrolysis with sodium methoxide gave alcohol **12**. Both (+)- and (-)-MTPA esters of the 5-hydroxy group of **12** were prepared to afford **13a** and **13b**, respectively. Resorting to proton NMR analysis of **13a** and **13b** showed that the Δδ values of H-2 - H-4 and H-22 - H23 were positive and the Δδ values of H-6 - H-10 were negative. The Δδ values obtained from these MTPA esters are shown in Fig. 5. Resorting to the systematic arrangement of positive and negative Δδ's enabled the *S* configuration at C-5 to be elucidated. According to the *cis* relationship of H-4 and H-5 on the lactone ring, the configuration of C-4 must be *S*.

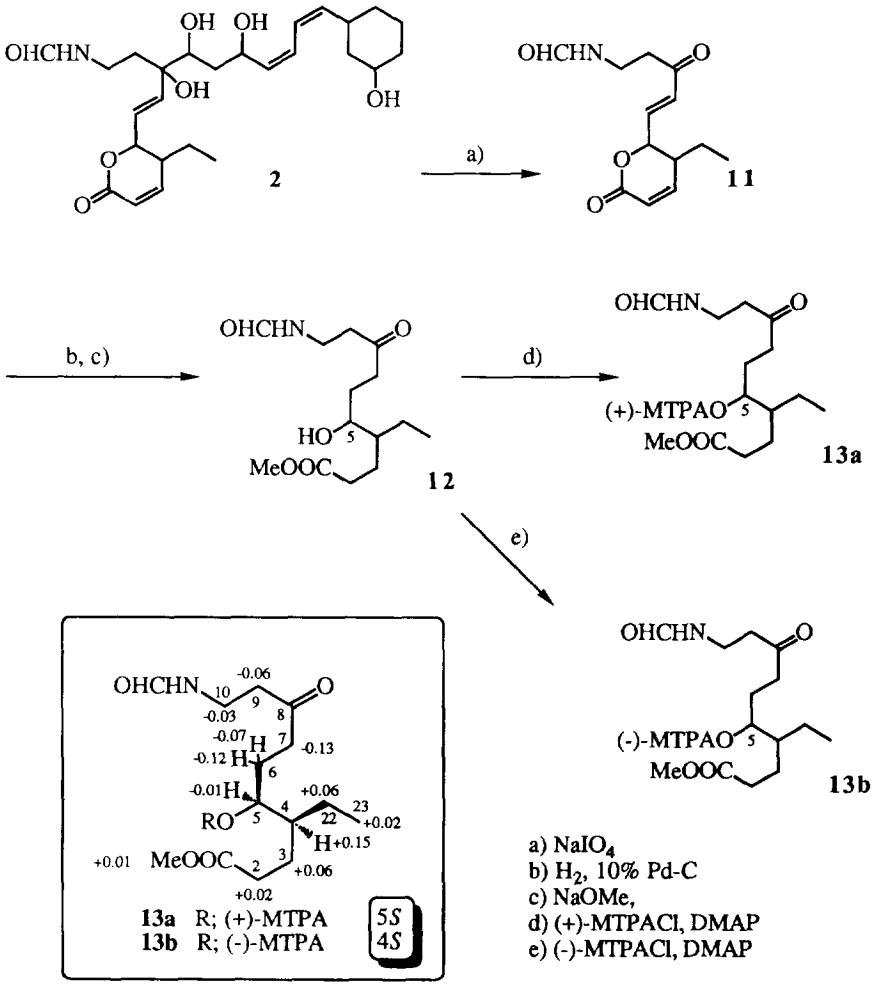

Fig.5. Preparation of **13a** and **13b**, and Δδ values obtained from **13a** and **13b**

In conclusion therefore, the absolute configuration of LSN-H was determined to be 4*S*, 5*S*, 8*R*, 9*R*, 11*R*, 16*R*, 18*S* by the modified Mosher's method as in Fig. 6. Since all LSNs and PLM-F have the same absolute configuration except for the stereochemistry on the acyl group at the cyclohexane ring, the absolute configurations of LSNs and PLM-F could also be determined.

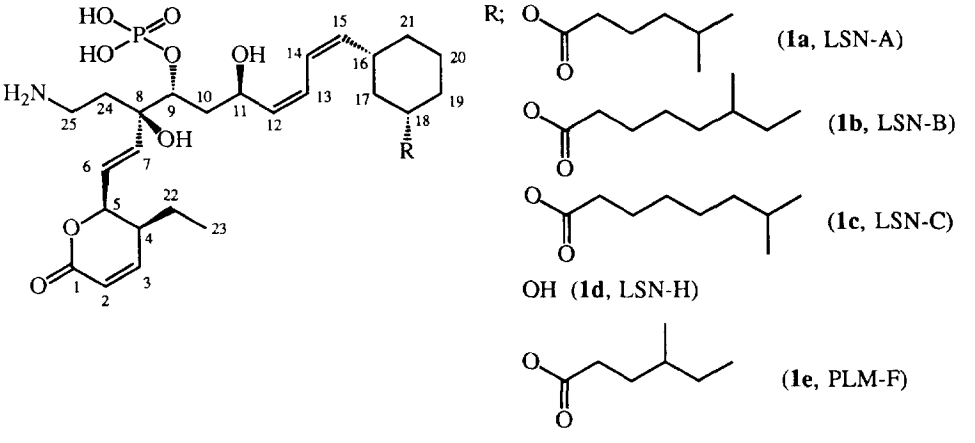

Fig.6. Absolute configuration of Leustroducsins and Phoslactomycin F

EXPERIMENTAL

IR spectra were measured on a JASCO FT/IR-830. NMR spectra were recorded on one of the following instruments: JEOL GSX-500, JEOL GSX-400, or JEOL JNM-EX 270. Chemical shifts are reported in ppm (δ) using TMS as an internal standard. FAB-MS and HR-FABMS were obtained using a JEOL JMS-AX505H. Silica gel 60 (230-400 mesh ASTM Merck) or Cosmosil 75C18-OPN (Nakarai Tesqui Inc.) was used as an adsorbent for column chromatography. Preparative thin layer chromatography was performed on Merck $60F_{254}$ (0.5mm or 2mm) precoated silica gel plates.

4-Ethyl-5-(3-(2-formylaminoethyl)-3,4,6-trihydroxy-10-(3-hydroxycyclohexyl)deca-1,7,9-trienyl)-2-penten-5-olide (**2**)

A mixture of LSN-H (2.95g, 5.57mmol), formamide (30ml) and phosphate buffer (pH=4, 0.1M, 30ml) was stirred at reflux temperature for 2 hours. After cooling, the mixture was poured into water and extracted with EtOAc. The extract was dried over magnesium sulfate and the solvent evaporated under reduced pressure. The residue obtained was loaded onto a Cosmosil column. The fraction eluted with MeOH was concentrated under reduced pressure. The residue obtained was loaded onto a silica gel column and the fraction eluted with EtOAc-MeOH (95:5) gave **2** (386mg, y. 15%) as a white powder.

IR (KBr) 3370, 1710, 1669 cm^{-1}. ^1H NMR (400MHz, CD_3OD) δ 0.96 (3H, t, J=7.5Hz), 0.95-1.20 (3H, m), 1.25-1.95 (11H, m), 2.50-2.60 (2H, m), 3.20-3.40 (2H, m), 3.55 (1H, tt, J=4.2, 10.9Hz), 3.70 (1H, dd, J=2.0, 10.1Hz), 4.80 (1H, m), 5.10 (1H, t, J=4.6Hz), 5.32 (1H, t, J=9.6Hz), 5.46 (1H, t, J=9.6Hz), 5.91 (1H, dd, J=4.6, 15.9Hz), 5.96 (1H, d, J=15.9Hz), 6.02 (1H, d, J=9.6Hz), 6.20-6.30 (2H, m), 7.09 (1H, dd, J=5.0, 9.6Hz), 7.99 (1H, s). FAB-MS (m/z) 478 $(M+H)^+$. HR-FABMS (m/z) Calcd for $C_{26}H_{40}NO_7$ $(M+H)^+$ 478.2805, Found 478.2801.

4-Ethyl-5-(3-(2-formylaminoethyl)-3,4,6-trihydroxy-10-(3-hydroxycyclohexyl)-3,4-O-isopropylidenedeca-1,7,9-trienyl)-2-penten-5-olide (**3**)

To a solution of **2** (197mg, 0.41mmol) in acetone (6ml), was added *p*-toluenesulfonic acid monohydrate (22mg, 0.12mmol). After being stirred for 2 hours at room temperature, the solvent was evaporated under reduced pressure and the residue obtained was purified by preparative thin layer silica gel chromatography (2mm, 20cm x 20cm, $CHCl_3$-MeOH 15:1) to afford **3** (112mg, y. 53%) as a white powder.

^1H NMR (270MHz, $CDCl_3$) δ 0.96 (3H, t, J=7.4Hz), 1.40 (3H, s), 1.52 (3H, s), 0.95-2.20 (16H, m), 2.45 (1H, m), 2.52 (1H, m), 3.27 (1H, m), 3.52 (1H, m), 3.63 (1H, m), 4.06 (1H, dd, J=2.6, 10.0Hz), 4.80 (1H, m), 5.04 (1H, t, J=4.2Hz), 5.39 (1H, br t, J=9.8Hz), 5.46 (1H, br t, J=9.8Hz), 5.88 (1H, d, J=15.5Hz), 5.95 (1H, dd, J=4.2, 15.5Hz), 6.06 (1H, d, J=9.8Hz), 6.19 (1H, br t, J=11.6Hz), 6.15-6.20 (1H, m), 6.30 (1H, br t, J=11.6Hz), 6.98 (1H, dd J=5.4, 9.8Hz), 8.11 (1H, s). FAB-MS (m/z) 518 $(M+H)^+$. HR-FABMS (m/z) Calcd for $C_{29}H_{44}NO_7$ $(M+H)^+$ 518.3118, Found 518.3125.

5-(3-(2-(N-p-bromobenzoyl-N-formylamino)ethyl)-3,4,6-trihydroxy-10-(3-hydroxycyclohexyl)-3,4-O-isopropylidenedeca-1,7,9-trienyl)-4-ethyl-2-penten-5-olide (**4**)

To a solution of **3** (9.1mg, 18μmol) in CH_2Cl_2 (1ml), were added triethylamine (7μl, 50μmol) and *p*-bromobenzoyl chloride (12mg, 55μmol), successively. After being stirred for 2.5 hours at room temperature, the solvent was evaporated under reduced pressure and the residue obtained was purified by preparative thin layer silica gel chromatography (0.5mm, 20cm x 20cm, CH_2Cl_2-MeOH 10:1) to afford **4** (9.1mg, y. 74%) as a white powder.

IR (KBr) 3435, 1724, 1665 cm^{-1}. ^1H NMR (270MHz, $CDCl_3$) δ 0.97 (3H, t, J=7.4Hz), 1.42 (3H, s), 1.56 (3H, s), 0.95-2.05 (16H, m), 2.40-2.60 (2H, m), 3.63 (1H, m), 3.77 (1H, m), 3.95-4.10 (2H, m), 4.80 (1H, m), 5.05 (1H, t, J=5.3Hz), 5.38 (1H, br t, J=9.8Hz), 5.46 (1H, br t, J=9.8Hz), 5.89 (1H, d, J=15.9Hz), 6.03 (1H, dd, J=5.3, 15.9Hz), 6.08 (1H, d, J=9.9Hz), 6.18 (1H, br t, J=11.6Hz), 6.30 (1H, br t, J=11.6Hz), 6.98 (1H, dd J=5.9, 9.9Hz), 7.41 (2H, d, J=8.3Hz), 7.65 (2H, d, J=8.3Hz), 8.88 (1H, s). FAB-MS (m/z) 700 $(M+H)^+$. HR-FABMS (m/z) Calcd for $C_{36}H_{47}NO_8Br$ $(M+H)^+$ 700.2485, Found 700.2472.

5-(3-(2-(N-p-bromobenzoyl-N-formylamino)ethyl)-3,4-dihydroxy-10-(3-hydroxycyclohexyl)-3,4-O-isopropylidene-6-(R)-(2-metoxy-2-phenyl-2-trifluoromethylacetoxy)deca-1,7,9-trienyl)-4-ethyl-2-penten-5-olide (**5a**)

To a solution of **4** (7.3mg, 10μmol) in CH_2Cl_2 (1ml), were added DMAP (3.9mg, 32μmol) and (+)-MTPA chloride (6μl, 32μmol), successively. After being stirred for 2 hours at room temperature, the solvent was evaporated under reduced pressure and the residue obtained was purified by preparative thin layer silica gel chromatography (0.5mm, 20cm x 20cm, CH_2Cl_2-MeOH 20:1) to afford **5a** (4.0mg, y. 42%) as a white powder.

IR ($CHCl_3$) 3436, 1725, 1668 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 0.87 (3H, t, J=7.3Hz), 1.31 (3H, s), 1.56 (3H, s), 0.90-2.05 (15H, m), 2.40 (1H, m), 2.53 (1H, m), 3.50 (3H, s), 3.62 (1H, m), 3.64 (1H, dd, J=2.0, 10.4Hz), 3.72 (1H, dt, J=4.3, 12.4Hz), 4.01 (1H, dt, J=4.3, 12.4Hz), 4.96 (1H, m), 5.36 (1H, br t, J=9.8Hz), 5.50 (1H, br t, J=9.8Hz), 5.71 (1H, d, J=15.6Hz), 5.97 (1H, dd, J=5.7, 15.6Hz), 6.04 (1H, m), 6.07 (1H, d, J=9.6Hz), 6.40 (1H, br t, J=11.6Hz), 6.44 (1H, br t, J=11.6Hz), 6.98 (1H, dd J=5.7, 9.6Hz), 7.30-7.43 (5H, m), 7.43-7.50 (2H, m), 7.64 (2H, d, J=8.6Hz), 8.87 (1H, s). FAB-MS (m/z) 938 $(M+Na)^+$. HR-FABMS (m/z) Calcd for $C_{46}H_{53}NO_{10}BrF_3Na$ $(M+Na)^+$ 938.2703, Found 938.2682.

5-(3-(2-(N-*p*-bromobenzoyl-N-formylamino)ethyl)-3,4-dihydroxy-10-(3-hydroxycyclohexyl)-3,4-O-isopropylidene-6-(*S*)-(2-metoxy-2-phenyl-2-trifluoromethylacetoxy)deca-1,7,9-trienyl)-4-ethyl-2-penten-5-olide (**5b**)

To a solution of **4** (9.1mg, 13μmol) in CH_2Cl_2 (1ml), were added DMAP (3.2mg, 26μmol) and (-)-MTPA chloride (5μl, 27μmol), successively. After being stirred for 2 hours at room temperature, the solvent was evaporated under reduced pressure and the residue obtained was purified by preparative thin layer silica gel chromatography (0.5mm, 20cm x 20cm, CH_2Cl_2-MeOH 20:1) to afford **5b** (6.0mg, y. 50%) as a white powder.

IR ($CHCl_3$) 3430, 1726, 1667 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 0.91 (3H, t, J=7.3Hz), 1.35 (3H, s), 1.58 (3H, s), 0.90-2.05 (15H, m), 2.40 (1H, m), 2.52 (1H, m), 3.48 (3H, s), 3.62 (1H, tt, J=4.3, 10.4Hz), 3.75 (1H, dt, J=4.3, 12.6Hz), 3.83 (1H, d, J=10.7Hz), 4.03 (1H, dt, J=4.3, 12.6Hz), 5.03 (1H, m), 5.28 (1H, br t, J=9.8Hz), 5.48 (1H, br t, J=9.8Hz), 5.84 (1H, d, J=15.4Hz), 6.02 (1H, dd, J=5.4, 15.4Hz), 6.03 (1H, m), 6.08 (1H, d, J=10.4Hz), 6.36 (1H, br t, J=11.6Hz), 6.40 (1H, br t, J=11.6Hz), 6.97 (1H, dd J=5.4, 9.6Hz), 7.35-7.45 (5H, m), 7.47 (2H, m), 7.64 (2H, d, J=8.2Hz), 8.87 (1H, s). FAB-MS (m/z) 938 $(M+Na)^+$. HR-FABMS (m/z) Calcd for $C_{46}H_{53}NO_{10}BrF_3Na$ $(M+Na)^+$ 938.2703, Found 938.2690.

5-(6-Benzoyloxy-3-(2-formylaminoethyl)-3,4-dihydroxy-10-(3-hydroxycyclohexyl)-3,4-O-isopropylidenedeca-1,7,9-trienyl)-4-ethyl-2-penten-5-olide (**6**)

To a solution of **3** (24.2mg, 47μmol) in CH_2Cl_2 (1ml), were added triethylamine (28μl, 0.20mmol), DMAP (3.0mg, 25μmol) and benzoyl chloride (23μl, 0.20mmol), successively. After being stirred for 2.5 hours at room temperature, the mixture was poured into H_2O and extracted with EtOAc. The extract was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue obtained was purified by preparative thin layer silica gel chromatography (2mm, 20cm x 20cm, CH_2Cl_2-MeOH 10:1) to afford **6** (9.5mg, y. 33%) as a white powder.

IR ($CHCl_3$) 3369, 1717, 1672 cm^{-1}. ^1H NMR (270MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.4Hz), 1.29 (3H, s), 1.50 (3H, s), 0.90-2.10 (15H, m), 2.36 (1H, m), 2.51 (1H, m), 3.20 (1H, m), 3.47-3.70 (2H, m), 3.87 (1H, dd, J=2.0, 8.2Hz), 4.99 (1H, t, J=3.6Hz), 5.40-5.50 (2H, m), 5.85-5.95 (2H, m), 6.05-6.18 (3H, m), 6.39 (1H, br t, J=11.6Hz), 6.42 (1H, br t, J=11.6Hz), 6.96 (1H, dd J=5.3, 9.9Hz), 7.43 (2H, d, J=7.3Hz), 7.55 (1H, t, J=7.3Hz), 8.02 (2H, d, J=7.3Hz), 8.12 (1H, s). FAB-MS (m/z) 622 $(M+H)^+$. HR-FABMS (m/z) Calcd for $C_{36}H_{48}NO_8$ $(M+H)^+$ 622.3380, Found 622.3385.

5-(6-Benzoyloxy-3-(2-formylaminoethyl)-3,4-dihydroxy-3,4-O-isopropylidene-10-(3-(*R*)-(2-methoxy-2-phenyl-2-trifluoromethylacetoxy)cyclohexyl)deca-1,7,9-trienyl)-4-ethyl-2-penten-5-olide (**8a**)

To a solution of **6** (7.8mg, 13μmol) in CH_2Cl_2 (1ml), were added DMAP (4.6mg, 38μmol) and (+)-MTPA chloride (6μl, 32μmol), successively. After being stirred for 3 hours at room temperature, the mixture was poured into H_2O and extracted with EtOAc. The extract was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography (CH_2Cl_2-MeOH 49:1) to afford **8a** (7.1mg, y. 68%) as a white powder.

IR ($CHCl_3$) 1722, 1686 cm^{-1}. ^1H NMR (500MHz, $CDCl_3$) δ 0.92 (3H, t, J=6.4Hz), 1.05 (1H, m), 1.25 (1H, m), 1.28 (3H, s), 1.42 (1H, m), 1.43 (1H, m), 1.44 (1H, m), 1.50 (3H, s), 1.54 (1H, m), 1.65 (1H, m), 1.67 (1H, m), 1.87 (1H, m), 1.87 (1H, m), 1.88 (1H, m), 1.96 (1H, m), 2.00 (1H, m), 2.09 (1H, m), 2.38 (1H, m), 2.62 (1H, m), 3.26 (1H, m), 3.55 (3H, s), 3.55 (1H, m), 3.86 (1H, dd, J=2.0, 8.2Hz), 4.99 (1H, dd J=4.0, 8.0Hz), 5.02 (1H, m), 5.40 (1H, br t, J=9.8Hz), 5.48 (1H, br t, J=9.8Hz), 5.89 (1H, d, J=15.3Hz), 5.95 (1H, dd, J=4.0, 15.3Hz), 6.05 (1H, m), 6.07 (1H, m), 6.07 (1H, d, J=9.8Hz), 6.39 (1H, br t, J=11.6Hz), 6.43 (1H, br t, J=11.6Hz), 6.94 (1H, dd J=5.5, 9.8Hz), 7.35-7.60 (8H, m), 8.02 (2H, d, J=7.3Hz), 8.11 (1H, s). FAB-MS (m/z) 860 $(M+Na)^+$. HR-FABMS (m/z) Calcd for $C_{46}H_{54}NO_{10}F_3Na$ $(M+Na)^+$ 860.3598, Found 860.3571.

5-(6-Benzoyloxy-3-(2-formylaminoethyl)-3,4-dihydroxy-3,4-O-isopropylidene-10-(3-(*S*)-(2-methoxy-2-phenyl-2-trifluoromethylacetoxy)cyclohexyl)deca-1,7,9-trienyl)-4-ethyl-2-penten-5-olide (**8b**)

To a solution of **6** (5.8mg, 9.3μmol) in CH_2Cl_2 (1ml), were added DMAP (3.0mg, 25μmol) and (-)-MTPA chloride (4μl, 21μmol), successively. After being stirred for 3 hours at room temperature, the mixture was poured into H_2O and extracted with EtOAc. The extract was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography (CH_2Cl_2-MeOH 49:1) to afford **8b** (4.1mg, y. 53%) as a white powder.

IR ($CHCl_3$) 3353, 1722, 1689, 1683 cm^{-1}. ^1H NMR (500MHz, $CDCl_3$) δ 0.92 (3H, t, J=6.4Hz), 1.04 (1H, m), 1.28 (3H, s), 1.32 (1H, m), 1.32 (1H, m), 1.41 (1H, m), 1.44 (1H, m), 1.49 (3H, s), 1.54 (1H, m), 1.66 (1H, m), 1.66 (1H, m), 1.84 (1H, m), 1.86 (1H, m), 1.88 (1H, m), 2.00 (1H, m), 2.01 (1H, m), 2.04 (1H, m), 2.38 (1H, m), 2.63 (1H, m), 3.25 (1H, m), 3.55 (3H, s), 3.55 (1H, m), 3.86 (1H, dd, J=2.0, 8.2Hz), 4.98 (1H, dd J=4.0, 8.0Hz), 5.02 (1H, m), 5.43 (1H, br t, J=9.8Hz), 5.48 (1H, br t, J=9.8Hz), 5.90 (1H, d, J=15.3Hz), 5.95 (1H, dd, J=4.0, 15.3Hz), 6.04 (1H, m), 6.07 (1H, m), 6.07 (1H, d, J=9.8Hz), 6.40 (1H, br t, J=11.6Hz), 6.44 (1H, br t, J=11.6Hz), 6.93 (1H, dd J=5.5, 9.8Hz), 7.38-

7.60 (8H, m), 8.02 (2H, d, J=7.3Hz), 8.12 (1H, s). FAB-MS (m/z) 838 $(M+H)^+$. HR-FABMS (m/z) Calcd for $C_{46}H_{55}NO_{10}F_3$ $(M+H)^+$ 838.3778, Found 838.3766.

5-(6-Benzoyloxy-10-(3-benzoyloxycyclohexyl)-3-(2-formylaminoethyl)-3,4-dihydroxydeca-1,7,9-trienyl)-4-ethyl-2-penten-5-olide (**9**)

To a solution of **2** (20mg, 42μmol) in CH_2Cl_2 (1ml), were added DMAP (22mg, 0.18mmol) and benzoyl chloride (12μl, 0.10mmol), successively. After being stirred for 2 hours at room temperature, the mixture was poured into H_2O and extracted with EtOAc. The extract was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue obtained was purified by preparative thin layer silica gel chromatography (0.5mm, 20cm x 20cm, CH_2Cl_2-MeOH 10:1) to afford **9** (8.8mg, y. 31%) as a white powder.

IR (KBr) 3383, 1716, 1671 cm^{-1}. ^1H NMR (270MHz, $CDCl_3$) δ 0.91 (3H, t, J=7.3Hz), 1.05-2.20 (15H, m), 2.42 (1H, m), 2.57-2.75 (1H, m), 3.10-3.65 (4H, m), 4,94-5.10 (2H, m), 5.45 (1H, br t, J=9.8Hz), 5.58 (1H, br t, J=9.8Hz), 5.82-5.96 (2H, m), 6.03 (1H, d, J=9.9Hz), 6.17 (1H, m), 6.24-6.35 (2H, m), 6.42 (1H, br t, J=11.6Hz), 6.92 (1H, dd, J=5.3, 9.9Hz), 7.40-7.50 (4H, m), 7.58 (2H, t, J=7.3Hz), 8.0-8.10 (5H, m). FAB-MS (m/z) 686 $(M+H)^+$. HR-FABMS (m/z) Calcd for $C_{40}H_{48}NO_9$ $(M+H)^+$ 686.3329, Found 686.3315.

5-(6-Benzoyloxy-10-(3-benzoyloxycyclohexyl)-3-(2-formylaminoethyl)-3-hydroxy-4-(*R*)-(2-methoxy-2-phenyl-2-trifluoromethylacetoxy)deca-1,7,9-trienyl)-4-ethyl-2-penten-5-olide (**10a**)

To a solution of **9** (4.3mg, 6.3μmol) in CH_2Cl_2 (1ml), were added DMAP (15mg, 0.12mmol) and (+)-MTPA chloride (15μl, 80μmol), successively. After being stirred for 2 hours at room temperature, the mixture was poured into H_2O and extracted with EtOAc. The extract was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue obtained was purified by preparative thin layer silica gel chromatography (0.5mm, 20cm x 20cm, CH_2Cl_2-MeOH 10:1) to afford **10a** (4.3mg, y. 76%) as a white powder.

IR ($CHCl_3$) 1720, 1687 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.3Hz), 1.05-1.75 (9H, m), 1.68 (1H, m), 1.86 (2H, m), 1.95-2.15 (2H, m), 2.26 (1H, m), 2.44 (1H, m), 2.61 (1H, m), 3.23 (1H, m), 3.45 (1H, m), 3.52 (1H, m), 3.54 (3H, s), 4.95 (1H, m), 4,99 (1H, m), 5.21 (1H, dd, J=2.1, 9.5Hz), 5.34 (1H, br t, J=9.8Hz), 5.38 (1H, br t, J=9.8Hz), 5.69 (1H, m), 5.90 (1H, d, J=15.3Hz), 6.00 (1H, m), 6.02 (1H, dd, J=5.3, 15.3Hz), 6.05 (1H, br t, J=11.6Hz), 6.06 (1H, d J=9.8Hz), 6.37 (1H, br t, J=11.6Hz), 6.92 (1H, dd, J=5.2, 9.8Hz), 7.37-7.50 (6H, m), 7.50-7.60 (4H, m), 8.0-8.05 (5H, m). FAB-MS (m/z) 924 $(M+Na)^+$. HR-FABMS (m/z) Calcd for $C_{50}H_{54}NO_{11}F_3Na$ $(M+Na)^+$ 924.3547, Found 924.3521.

5-(6-Benzoyloxy-10-(3-benzoyloxycyclohexyl)-3-(2-formylaminoethyl)-3-hydroxy-4-(*S*)-(2-methoxy-2-phenyl-2-trifluoromethylacetoxy)deca-1,7,9-trienyl)-4-ethyl-2-penten-5-olide (**10b**)

To a solution of **9** (4.4mg, 6.4μmol) in CH_2Cl_2 (1ml), were added DMAP (12mg, 98μmol) and (-)-MTPA chloride (12μl, 64μmol), successively. After being stirred for 2 hours at room temperature, the mixture was poured into H_2O and extracted with EtOAc. The extract was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue obtained was purified by preparative thin layer silica gel chromatography (0.5mm, 20cm x 20cm, CH_2Cl_2-MeOH 10:1) to afford **10b** (4.5mg, y. 78%) as a white powder.

IR ($CHCl_3$) 1718, 1688 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 0.90 (3H, t, J=7.3Hz), 1.05-1.75 (10H, m), 1.72 (1H, m), 1.87 (1H, m), 2.00-2.15 (2H, m), 2.32 (1H, m), 2.41 (1H, m), 2.63 (1H, m), 3.17 (1H, m), 3.40 (1H, m), 3.48 (3H, s), 3.50 (1H, m), 4.95 (1H, m), 5.00 (1H, m), 5.18 (1H, dd, J=2.1, 8.8Hz), 5.39 (1H, br t, J=9.8Hz), 5.41 (1H, br t, J=9.8Hz), 5.77 (1H, m), 5.83 (1H, d, J=15.3Hz), 5.95 (1H, m), 5.97 (1H, dd, J=5.4, 15.3Hz), 6.04 (1H, d, J=9.8Hz), 6.11 (1H, br t, J=11.6Hz), 6.39 (1H, br t, J=11.6Hz), 6.90 (1H, dd, J=5.0, 9.8Hz), 7.40-7.50 (6H, m), 7.50-7.60 (4H, m), 8.00-8.05 (5H, m). FAB-MS (m/z) 924 $(M+Na)^+$. HR-FABMS (m/z) Calcd for $C_{50}H_{54}NO_{11}F_3Na$ $(M+Na)^+$ 924.3547, Found 924.3541.

4-Ethyl-5-(5-formylamino-3-ketopent-1-enyl)-2-penten-5-olide (**11**)

To a solution of **2** (124mg, 0.26mmol) in MeOH (1ml), was added a solution of $NaIO_4$ (56mg, 0.26mmol) in H_2O (1ml). After being stirred for 2 hours at room temperature, the mixture was poured into H_2O and extracted with EtOAc. The extract was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography (CH_2Cl_2-MeOH 49:1) to afford **11** (58mg, y. 89%) as a white powder.

IR ($CHCl_3$) 3339, 1725, 1675 cm^{-1}. ^1H NMR (270MHz, $CDCl_3$) δ 0.96 (3H, t, J=7.4Hz), 1.40-1.65 (2H, m), 2.53 (1H, m), 2.88 (2H, t, J=5.7Hz), 3.61 (2H, q, J=5.7Hz), 5.19 (1H, m), 6.09 (1H, d, J=9.8Hz), 6.29 (1H, m), 6.56 (1H, dd, J=2.0, 15.8Hz), 6.79 (1H, dd, J=4.0, 15.8Hz), 7.04 (1H, dd, J=5.6, 9.8Hz), 8.13 (1H, s). FAB-MS (m/z) 252 $(M+H)^+$. HR-FABMS (m/z) Calcd for $C_{13}H_{18}NO_4$ $(M+H)^+$ 252.1236, Found 252.1222.

Methyl 4-ethyl-10-formylamino-5-hydroxy-8-ketodecanate (**12**)

A mixture of **11** (20mg, 80μmol), 10% Pd-C (5mg) and EtOAc (2ml) was stirred under H_2 at room temperature for 45 min. The catalyst was removed by Celite filtration. The filtrate was concentrated under reduced pressure. The residue obtained was taken up into MeOH (1ml) and treated with NaOMe (29mg) at room temperature for 15 min. The mixture was poured into aq NH_4Cl and extracted with EtOAc. The extract was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford crude **12** (17.9mg), which was used in the next step without purification.

Methyl 4-ethyl-10-formylamino-8-keto-5-(R)-(2-methoxy-2-phenyl-2-trifluoromethylacetoxy)decanate (**13a**)

To a solution of crude **12** (7.6mg, 26μmol) in CH_2Cl_2 (1ml), were added DMAP (21.5mg, 0.18mmol) and (+)-MTPA chloride (35μl, 0.19mmol), successively. After being stirred for 1 hour at room temperature, the mixture was poured into aq NH_4Cl and extracted with EtOAc. The extract was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography (CH_2Cl_2-MeOH 49:1) to afford **13a** (6.0mg, y. 36% from **11**) as a white powder.

IR ($CHCl_3$) 3370, 1740, 1718, 1683 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 0.91 (3H, t, J=7.4Hz), 1.28 (2H, m), 1.38 (1H, m), 1.53 (2H, m), 1.85 (1H, m), 1.96 (1H, m), 2.25 (2H, t, J=7.4Hz), 2.38 (2H, t, J=7.0Hz), 2.60 (2H, t, J=5.6Hz), 3.52 (3H, s), 3.53 (2H, m), 3.65 (3H, s), 5.14 (1H, m), 6.11 (1H, m), 7.40-7.47 (3H, m), 7.52-7.55 (2H, m), 8.11 (1H, s). FAB-MS (m/z) 504 $(M+H)^+$. HR-FABMS (m/z) Calcd for $C_{24}H_{33}NO_7F_3$ $(M+H)^+$ 504.2209, Found 504.2213.

Methyl 4-ethyl-10-formylamino-8-keto-5-(S)-(2-methoxy-2-phenyl-2-trifluoromethylacetoxy)decanate (**13b**)

To a solution of crude **12** (10.3mg, 36μmol) in CH_2Cl_2 (1ml), were added DMAP (24mg, 0.20mmol) and (-)-MTPA chloride (36μl, 0.19mmol), successively. After being stirred for 1 hour at room temperature, the mixture was poured into aq NH_4Cl and extracted with EtOAc. The extract was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography (CH_2Cl_2-MeOH 49:1) to afford **13b** (9.7mg, y. 42% from **11**) as a white powder.

IR ($CHCl_3$) 3369, 1739, 1717, 1683 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 0.93 (3H, t, J=7.4Hz), 1.34 (2H, m), 1.53 (1H, m), 1.59 (2H, m), 1.73 (1H, m), 1.89 (1H, m), 2.25 (2H, t, J=7.0Hz), 2.27 (2H, t, J=7.4Hz), 2.54 (2H, t, J=5.6Hz), 3.52 (3H, s), 3.50 (2H, m), 3.66 (3H, s), 5.13 (1H, m), 6.10 (1H, m), 7.40-7.47 (3H, m), 7.52-7.55 (2H, m), 8.11 (1H, s). FAB-MS (m/z) 504 $(M+H)^+$. HR-FABMS (m/z) Calcd for $C_{24}H_{33}NO_7F_3$ $(M+H)^+$ 504.2209, Found 504.2203.

REFERENCES

1. Metcalf, D. *Nature* **1994**, *369*, 519.
2. a) Sauvage, F. J.; Hass, P. E.; Spencer, S. D.; Malloy, B. E.; Gurney, A. L.; Spencer, S. A.; Darbonne, W. C.; Henzel, W. J.; Wong, S. C; Kuang, W. J. *Nature* **1994**, *369*, 533. b) Lok, S.; Kaushansky, K.; Holly, R. D.; Kuijper, J. L.; Lofton, D. C.; Oort, P. J.; Grant, F. J.; Heipel, M. D.; Burkhead, S. K.; Kramer, J. M. *Nature* **1994**, *369*, 565. c) Wendling, F.; Maraskovsky, E.; Debili, N.; Florindo, C.; Teepe, M.; Titeux, M.; Methia, N.; Breton, G. J.; Cosman, D.; Vainchenker, W. *Nature* **1994**, *369*, 571. d) Sohma, Y.; Akahori, H.; Seki, N.; Hori, T.; Ogami, K.; Kato, T.; Shimada, Y.; Kawamura, K.; Miyazaki, H. *Febs Lett.*, **1994**, *353*, 57.
3. Maeda, M.; Suzuki, S.; Ohtsuka, K.; Satoh, S.; Nishigaki, F.; Shimomura, K.; Imai, Y.; Niwa, M.; Kohsaka, M. *Biol. Pharm. Bull.*, **1994**, *17*, 173.
4. a) Kohama, T.; Enokita, R.; Okazaki, T.; Miyaoka, H.; Torikata, A.; Inukai, M.; Kaneko, I.; Kagasaki,

T.; Sakaida, Y.; Satoh, A.; Shiraishi, A. *J. Antibiot.*, **1993**, *46*, 1503. b) Kohama, T.; Nakamura, T.; Kinoshita, T.; Kaneko, I.; Shiraishi, A. *J. Antibiot.*, **1993**, *46*, 1512.

5. a) Fushimi, S.; Nishikawa, S.; Shimazu, A.; Seto, H. *J. Antibiot.*, **1989**, *42*, 1019. b) Fushimi, S.; Furihata, K.; Seto, H. *J. Antibiot.*, **1989**, *42*, 1026.
6. Kohama, T.; Maeda, H.; Shiraishi, A.; Yamashita, K. *J. Antibiot.*, submitted.
7. Kohama, T.; Koishi, T.; Kono, K.; Asai, F.; Shiraishi, A.; Maeda, H.; Sasagawa, K.; Kobayashi, T.; Yamashita, K.; Kurihara, S.; Shibata, T.; Ishibashi, T. BMP Japan 95, 1995; Abstract No. P4-5, Oiso.
8. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.*, **1991**, *113*, 4092.
9. Kaneko, M.; Kimura, M.; Nishimura, T.; Shimizu, B. *Chem. Pharm. Bull.*, **1977**, *25*, 2482.

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A Catalytic Enantioselective Reaction Using a C_2-Symmetric Disulfonamide as a Chiral Ligand: Simmons-Smith Cyclopropanation of Allylic Alcohols by the Et_2Zn-CH_2I_2-Disulfonamide System

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Abstract: *A catalytic and enantioselective Simmons-Smith cyclopropanation of an allylic alcohol was developed by the reaction of an allylic alcohol with Et_2Zn and CH_2I_2 in the presence of a catalytic amount of chiral disulfonamide* ***4****.*

The development of catalytic and enantioselective reactions has been one of the most important and challenging topics in organic synthesis. As one approach to solve this problem, we[2] and Corey *et al.*[3] have independently demonstrated the potential utility of Lewis acid catalysts modified by electron-withdrawing chiral disulfonamides. In this paper is described the full detail of the catalytic and enantioselective Simmons-Smith cyclopropanation of disubstituted allylic alcohols in the presence of a catalytic amount of disulfonamide-modified zinc complex.[4]

Among the various types of catalytic, enantioselective reaction investigated, cyclopropanation has attracted continuing and increasing attention since the pioneering work by Nozaki *et al.* in 1966,[5] and, indeed, reactions catalyzed by bis(oxazoline)copper complexes were independently reported by Masamune *et al.*[6a] and Evans *et al.*[6b] Further, bis(oxazolinyl)pyridine-ruthenium catalyst was recently reported by Nishiyama *et al.*[6c] However, the carbene sources employed in previous studies have been limited to diazoacetate derivatives, and there have been no examples using the Simmons-Smith type of reagent. Independent of our work, Ukaji *et al.*[7] and Denmark *et al.*[8] reported the enantioselective Simmons-Smith reaction in 1992. Further, highly enantioselective chiral boron complex was also developed by Charette *et al.*[9] These methodologies, however, require a stoichiometric amount of chiral auxiliaries, and to our knowledge there has been no catalytic and enantioselective Simmons-Smith reaction except our method utilizing disulfonamide-modified metal complexes. Improvement of our method[4] has very recently been reported by Denmark *et al.*[10], which also prompted us to describe our own results.

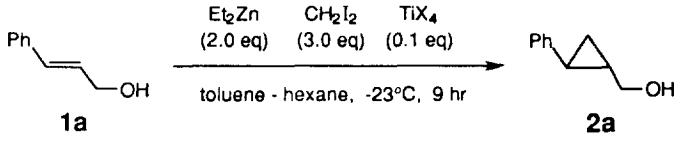
It is well recognized that the Simmons-Smith reaction of an allylic alcohol or its ether derivative proceeds much faster than that of a simple olefin,[11] and this enhancement of reactivity is explained by considering the proximity effect attributed to the strong affinity between the organozinc reagent and the oxygen atom.[12]

On the other hand, Friedrich *et al.* observed that the addition of catalytic amount of titanium tetrachloride facilitates the Simmons-Smith reaction of a simple olefin such as cyclohexene and α-pinene.[13] Although the function of titanium tetrachloride is not clear, we assumed that one possibility might be due to the activation of the carbenoid.

Based on these facts, we became interested in examining the Simmons-Smith reaction of an allyl alcohol derivative in the presence of a disulfonamide-modified Lewis acid catalyst. Carbene source employed in the present study is diethylzinc-methylene iodide developed by Furukawa *et al.*[14]

Since there has been only one example of the Lewis acid-mediated Simmons-Smith reaction,[13] we initially carried out the cyclopropanation of cinnamyl alcohol **1a** in the presence of $Ti(O\text{-}i\text{-}Pr)_4$ or $TiCl_4$.

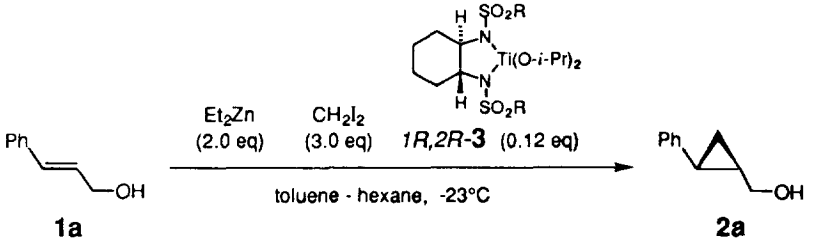
Scheme 1



TiX_4 (Yield): none (22%), $Ti(O\text{-}i\text{-}Pr)_4$ (35%), $TiCl_4$ (77%)

The results shown in Scheme 1 clearly demonstrate that the cyclopropanation of an allylic alcohol is indeed facilitated by Lewis acid. Encouraged with these results, we then examined the cyclopropanation of cinnamyl alcohol **1a** in the presence of disulfonamide-modified titanium catalyst which we have shown to be an excellent catalyst for the alkylation of an aldehyde with dialkylzinc.[2] The chiral tiatanium catalysts **3** were prepared *in situ* according to our original procedure.[2] Cyclopropanation proceeded smoothly to afford the cyclopropane **2a** in good yields. However, the enantioselectivities were found very poor as shown in Table 1.

Table 1



Entry	3	R	Time (h)	Yield (%)	e.e. (%)
1	3a	α-naphthyl	10	70	7
2	3b	CF_3	9	82	16
3	3c	$n\text{-}C_4F_9$	9	58	~0

After extensive experimentations, disulfonamide-modified zinc complex was found effective in Simmons-Smith reaction which was described below.