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Supporting Information

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Asymmetric Total Synthesis of (-)-Merrilactone A: Use of Bulky Protective Group as Long-Range Stereocontrolling Element

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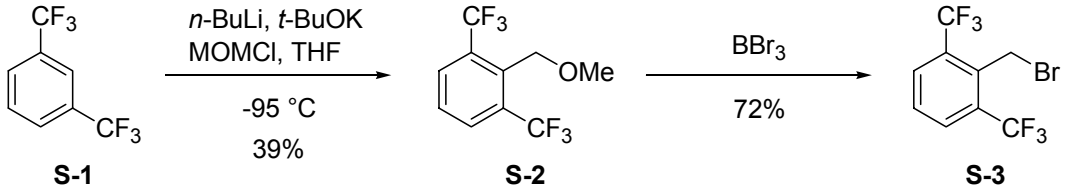
General Methods. All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. THF was distilled from sodium/benzophenone, diethyl ether from $LiAlH_4$, dichloromethane, pyridine, triethylamine, and toluene from calcium hydride, and DMF and DMSO from calcium hydride under reduced pressure. All other reagents were used as supplied unless otherwise stated. Analytical thin-layer chromatography (TLC) was performed using E. Merck Silica gel 60 F254 pre-coated plates. Column chromatography was performed using 100-210 μm Silica Gel 60N (Kanto Chemical Co., Inc.), and for flash chromatography 40-50 μm Silica Gel 60N (Kanto Chemical Co., Inc.) was used. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian INOVA 500 (500 MHz) or JEOL JNM-ECA-600 (600 MHz) spectrometer. Chemical shifts are reported in δ (ppm) with reference to solvent signals [^{1}H-NMR: $CHCl_3$ (7.26), C_6HD_5 (7.15), CHD_2OD (3.31); ^{13}C-NMR: $CDCl_3$ (77.0), C_6D_6 (128.0), CD_3OD (49.0)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer. EI mass spectra were measured on a HITACHI M-2500S (HRMS) and ESI-TOF mass spectra were recorded on

a BRUKER DALTONICS APEX III (HRMS). Melting points were measured on a Yanaco MP-S3 micro melting point apparatus. Optical rotations were recorded on JASCO DIP-370 polarimeter.

Synthesis of 2,6-bis(trifluoromethyl)benzyl bromide (BTBBr) S-3



2,6-bis(trifluoromethyl)benzyl methyl ether S-2.[1] To a cooled solution (–30 ºC) of *t*-BuOK (176 g, 1.57 mol) in THF (2.1 L) was added 1,3-bis(trifluoromethyl)benzene **S-1** (163 mL, 1.05 mol). The mixture was cooled to –95 ºC over 1 h, and then *n*-BuLi in hexane (1.57 M, 1.0 L, 1.57 mol) was added at a rate sufficient to maintain the temperature below –85 ºC over 1.5 h. After the mixture was stirred at –95 ºC for 7 h, MOMCl (159 mL, 2.10 mol) was added dropwise over 1.5 h. Then the reaction mixture was allowed to warm to room temperature, stirred for 13 h and quenched with H_2O. The aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The resultant solution was distillated under reduced pressure to give 105 g of **S-2** (39%): colorless oil; b.p. 58 ºC/0.2 mmHg; IR (film) 1598, 1174, 1134 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.44 (s, 3H), 4.67 (s, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 58.8, 66.5, 123.7 (q, J = 273 Hz, 2C), 128.7, 130.0 (q, J = 5.8 Hz, 2C), 132.0 (q, J = 30.5 Hz, 2C), 135.2; HRMS (EI), calcd for $C_{10}H_8F_6O$ M^+ 258.0479, found 258.0480.

2,6-bis(trifluoromethyl)benzyl bromide S-3. **S-2** was charged in a flask and cooled to –40 ºC, and

(1) (a) Schlosser, M.; Katsoulos, G.; Takagishi, S. *Synlett* **1990**, 747. (b) Dmowski, W.; Piasecka-Maciejewska, K. *Tetrahedron*, **1998**, *54*, 6781.

then BBr_3 (42.3 mL, 448 mmol) was added. The mixture was warmed to room temperature, and stirred for 2 h. After being cooled to 0 ºC, the solution was diluted with hexane and quenched with H_2O. The aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The resultant solution was distillated under reduced pressure to give 89.9 g of **S-3** (72%): colorless oil; b.p. 65 ºC/4.0 mmHg; IR (film) 1597, 1178, 1132 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.78 (s, 2H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.1, 123.5 (q, *J* = 274 Hz, 2C), 129.0, 13.0.5 (q, *J* = 5.8 Hz, 2C), 131.2 (q, *J* = 30.5 Hz, 2C), 135.3; HRMS (EI), calcd for $C_9H_5BrF_6$ M^+ 305.9479, found 305.9478.

Alcohol 10. To a cooled suspension of $LiAlH_4$ (34.0 g, 895 mmol) in DME (500 mL) was added a solution of *t*-butanol (257 mL, 2.69 mmol) in DME (500 mL) at 0 ºC. The resulting suspension of $LiAlH(Ot\text{-}Bu)_3$ in DME was added dropwise over 20 min to a solution of 2,3-dimethylmaleic anhydride **9** (82.1 g, 651 mmol) in DME (1.70 L) at –15 ºC. The mixture was stirred at –15 ºC for 1 h and then at room temperature for 1 h, quenched with 2 M HCl, and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The obtained solid was recrystallized from a mixture of EtOAc (30 mL) and hexane (30 mL) to give 88.7 g of **10** (85%): colorless crystal; m.p. 79-80 ºC; R_f = 0.38 (silica gel, 1:1 hexane/EtOAc); IR (film) 3364, 1736, 1087, 971 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.82 (s, 3H), 2.00 (s, 3H), 4.27 (d, *J* = 7.0 Hz, 1H), 5.88 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.2, 11.4, 98.7, 125.6, 156.7, 173.7; HRMS (EI), calcd for $C_6H_8O_3$ M^+ 128.0473, found 128.0473.

Methyl ester 11. To a cooled suspension of $Ph_3PCH_3^+Br^-$ (148 g, 414 mmol) in THF (500 mL) was added dropwise *t*-BuOK (46.5 g, 414 mmol) at 0 ºC. The yellow mixture was stirred at room temperature for 3 h and cooled to 0 ºC. To the mixture was added a solution of **10** (26.5 g, 207 mmol) in THF (200 mL). The reaction mixture was stirred for 1 h at 0 ºC and for 1 h at room temperature

and Et_2O was added. The organic layer was extracted with 10% aqueous K_2CO_3. The aqueous layer was acidified with 2 M HCl and extracted four times with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified with open column chromatography (hexane/Et_2O 3:1 to 1:3) to give 22.7 g of an acid (87%): colorless crystal; m.p. 71-72 ºC; R_f = 0.44 (silica gel, 1:1 hexane/EtOAc); IR (film) 2954, 1678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.96 (s, 3H), 2.02 (s, 3H), 5.27 (d, *J* = 11.0, 1H), 5.47 (d, *J* = 17.5 Hz, 1H), 7.38 (dd, *J* = 17.5, 11.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.4, 16.5, 117.2, 125.3, 136.0, 143.3, 175.0; HRMS (EI), calcd for $C_7H_{10}O_2$ M^+ 126.0681, found 126.0685.

To a solution of the above acid (135 g, 1.07 mol) in THF (3.4 L) were added MeI (200 mL, 3.21 mol) and K_2CO_3 (296 g, 2.14 mol). After being heated to 50 ºC, the reaction mixture was stirred for 16 h and diluted with H_2O. The aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The resultant solution was distilled under reduced pressure to give 138 g of **11** (92%): colorless oil; b.p. 52 ºC/0.4 mmHg; R_f = 0.71 (silica gel, 1:1 hexane/EtOAc); IR (film) 1715, 1234, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.90 (s, 3H), 1.98 (s, 3H), 3.76 (s, 3H), 5.20 (d, *J* = 11.0 Hz, 1H), 5.39 (d, *J* = 17.5 Hz, 1H), 7.08 (dd, *J* = 17.5, 11.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5, 16.6, 51.6, 116.2, 126.6, 135.9, 139.6, 170.1; HRMS (EI), calcd for $C_8H_{12}O_2$ M^+ 140.0837, found 140.0833.

Hydroxy γ-lactone 12. To a flask equipped with a mechanical stirrer were added AD-mix-α (252 g), H_2O (935 mL) and *t*-BuOH (500 mL). After being cooled to 0 ºC over 30 min, a solution of **11** (26.2 g, 187mmol) in *t*-BuOH (435 mL) was added to the above solution dropwise. The mixture was stirred vigorously at 0 ºC for 17 h and quenched with saturated aqueous thiosulfate. The aqueous layer was extracted three times with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified with open column chromatography (hexane/EtOAc 1:1 to EtOAc) to give 23.9 g of **12** (90%, 90%ee). The resultant solid was

recrystallized from a mixture of Et_2O (70 mL) and CH_2Cl_2 (0.5 mL) to give 17.4g of **12** (65%, 99%ee): colorless crystal; m.p. 44-45 ºC, R_f = 0.24 (silica gel, 1:1 hexane/EtOAc); $[\alpha]^{25}_D$ –0.02 (*c* 1.08, $CHCl_3$); IR (film) 3436, 2927, 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.83 (m, 3H), 2.00 (m, 3H), 3.72 (dd, *J* = 12.5, 5.0 Hz, 1H), 4.05 (dd, *J* = 12.5, 3.0 Hz, 1H), 4.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.4, 12.0, 61.4, 84.0, 124.8, 156.7, 174.7; HRMS (EI), calcd for $C_7H_{10}O_3$ M^+ 142.0630, found 142.0629.

The enantiomeric excess of the recrystallized **12** was determined by ^1H-NMR of (+)-MTPA-ester. (+)-MTPACl (30.5 μL, 163 μmol) was added to a solution of recrystallized **12** (11.1 mg, 81.6 μmol) and DMAP (29.9 mg, 245 μmol) in CH_2Cl_2 (2.7 mL). The mixture was stirred for 1 h and quenched with saturated ammonium chloride. The aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated: **(+)-MTPA-12**: colorless oil; R_f = 0.41 (silica gel, 1:1 hexane/EtOAc); IR (film) 1755, 1170 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.72 (m, 3H), 1.90 (m, 3H), 3.49 (s, 3H), 4.49 (dd, *J* = 12.0, 3.5 Hz, 1H), 4.71 (dd, *J* = 12.0, 3.5 Hz, 1H), 4.95 (m, 1H), 7.42 (m, 5H); HRMS (ESI), calcd for $C_{17}H_{17}F_3O_5Na$ $(M+Na)^+$ 381.0926, found 381.0922.(-)-MTPACl (25.2 μL, 135 μmol) was added to a solution of recrystallized **12** (6.4 mg, 45.0 μmol) and DMAP (22.0 mg, 180 μmol) in CH_2Cl_2 (2.3 mL). The mixture was stirred for 1 h and quenched with saturated ammonium chloride. The aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated: **(-)-MTPA-12**: colorless oil; R_f = 0.41 (silica gel, 1:1 hexane/EtOAc); IR (film) 1752, 1170 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.77 (m, 3H), 1.96 (m, 3H), 3.48 (s, 3H), 4.48 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.69 (dd, *J* = 12.0, 3.0 Hz, 1H), 4.94 (m, 1H), 7.44 (m, 5H); HRMS (ESI), calcd for $C_{17}H_{17}F_3O_5Na$ $(M+Na)^+$ 381.0926, found 381.0922.

Pivaloate ester 13. To a solution of **12** (40.8 g, 287 mmol) in CH_2Cl_2 were added pyridine (37.2 mL, 459 mmol), DMAP (4.56 g, 37.3 mmol) and PivCl (49.5 mL, 401 mmol). The reaction mixture was stirred at room temperature for 18 h and diluted with 1 M HCl. The aqueous layer was extracted with

CH_2Cl_2 and Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified with flash column chromatography (hexane/ EtOAc 9:1 to 1:1) to give 42.8 g of **13** (99%): colorless crystal; m.p. 32-33 ºC; R_f = 0.38 (silica gel, 1:1 hexane/EtOAc); $[\alpha]^{24}_D$ –49.6 (*c* 1.21, $CHCl_3$); IR (film) 2975, 1758, 1732, 1154 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 9H), 1.83 (dq, J = 2.0, 1.0 Hz, 3H), 1.99 (dq, *J* = 1.5, 1.0 Hz, 3H), 4.30 (dd, *J* = 12.5, 4.0 Hz, 1H), 4.41 (dd, *J* = 12.5, 3.0 Hz, 1H), 4.90 (ddqq, *J* = 4.0, 3.0, 2.0, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.4, 12.0, 27.0, 38.8, 61.6, 80.9, 125.4, 155.3, 173.8, 177.9; HRMS (ESI), calcd for $C_{12}H_{18}O_4Na$ $(M+Na)^+$ 249.1103, found 249.1097.

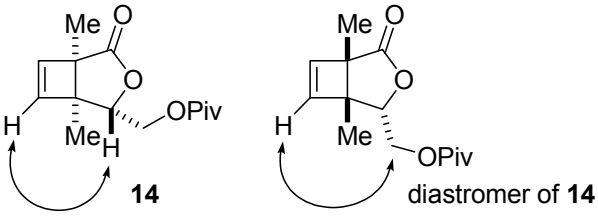
Triol 15. A solution of **13** (10.0 g, 44.2 mmol) and *cis*-1,2-dichloroehtylene (50.1 mL, 663 mmol) in CH_3CN (1.0 L) was placed in a photochemical reactor (two-necked vessel equipped with a Quartz immersion type cooling jacket). The reactor was placed into a cooled bath (–20 ºC) and a stream of MeOH at –20 ºC was circulated through the jacket. The reaction mixture was irradiated using HANAU (400W high pressure mercury lamp) for 2 d. The solvent was concentrated to give a crude dichlorocyclobutane (14.9 g), which was used directly in the next reaction.

Zinc dust was successively washed with 2% HCl, water, ethanol, and diethyl ether, and then dried under reduced pressure. The freshly activated zinc (57.8 g, 884 mmol) was added into a flask equipped with a mechanical stirrer, and toluene (50 mL) was then introduced. To the suspension was added a solution of dichlorocyclobutane in toluene (38 mL) and acetic anhydride (54.2 mL). The mixture was stirred at 120 ºC for 1 d, and concentrated to give a crude mixture of **14** and its facial diastereomer (21.2 g), which was used directly in the next reaction.

To determine the stereochemistry, the two diastereomers were separated by HPLC (YMC-Pack R&D SIL-06, 250x20 mm, UV 200 nm, hexane/*i*-PrOH 19:1, 10.0 mL/min, **14**: T_R = 30 min, its diastereomer: T_R = 19 min): **14**: colorless oil; R_f = 0.31 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{24}_D$ –130.9 (*c* 1.32, $CHCl_3$); IR (film) 2974, 1767, 1735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.26 (s,

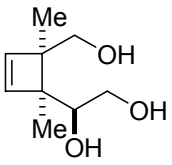
3H), 1.35 (s, 3H), 3.99 (dd, J = 12.5, 3.0 Hz, 1H), 4.37 (dd, J = 12.5, 3.5 Hz, 1H), 4.54 (dd, J = 3.5, 3.0 Hz, 1H), 6.24 (d, J = 2.5 Hz, 1H), 6.33 (d, J = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.0, 14.3, 27.1, 38.7, 51.3, 54.6, 63.2, 78.0, 141.9, 144.2, 178.0, 178.1; HRMS (ESI), calcd for $C_{14}H_{20}O_4Na$ $(M+Na)^+$ 275.1259, found 275.1254. **diastereomer of 14**: colorless oil; R_f = 0.41 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{18}_D$ +91.2 (*c* 1.04, $CHCl_3$); IR (film) 2973, 1770, 1732 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 0.67 (s, 3H), 0.97 (s, 3H), 1.16 (s, 9H), 3.76 (dd, J = 7.5, 4.5 Hz, 1H), 3.97 (dd, J = 12.0, 7.5 Hz, 1H), 4.05 (dd, J = 12.0, 4.5 Hz, 1H), 5.51 (d, J = 3.0 Hz, 1H), 5.74 (d, J = 3.0 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.9, 17.7, 27.1, 38.8, 51.9, 55.2, 62.9, 79.6, 140.9, 142.5, 177.4, 178.2; HRMS (ESI), calcd for $C_{14}H_{20}O_4Na$ $(M+Na)^+$ 275.1259, found 275.1253.

NOE data of cyclobutene **14** (500 MHz, $CDCl_3$) and its diastereomer (500 MHz, C_6D_6)



To a suspension of $LiAlH_4$ (13.4 g, 354 mmol) in Et_2O (150 mL) was added the above mixture of **14** and its diastereomer in Et_2O (150 mL). The reaction mixture was stirred at room temperature for 2 h, quenched with 2 M HCl. The aqueous layer was extracted with EtOAc six times. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified with flash column chromatography (hexane/ EtOAc 1:1 to EtOAc) to give 5.68 g of **15** (75% for 3 steps), along with 580 mg of its diastereomer (8% for 3 steps): **15**: yellow amorphous solid; R_f = 0.26 (silica gel, EtOAc); $[\alpha]^{25}_D$ +5.5 (*c* 1.16, $CHCl_3$); IR (film) 3321, 2960 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.22 (s, 3H), 3.47 (d, J = 11.5 Hz, 1H), 3.61 (dd, J = 10.5, 8.0 Hz, 1H), 3.62 (dd, J = 10.5, 4.0 Hz, 1H), 3.80 (bs, 3H), 3.95 (d, J = 11.5 Hz, 1H), 4.03 (dd, J = 8.0, 4.0 Hz, 1H), 5.95 (d, J = 3.0 Hz, 1H), 6.00 (d, J = 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 18.9, 53.5, 53.9, 63.9,

67.6, 75.8, 140.5, 141.1; HRMS (ESI), calcd for $C_9H_{16}O_3Na$ $(M+Na)^+$ 195.0997, found 195.0993. **diastereomer of 15**: yellow amorphous solid; R_f = 0.13 (silica gel, EtOAc); $[\alpha]^{25}_D$ +5.1 (*c* 0.59, CH_3OH); IR (film) 3267, 3199, 1010 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.09 (s, 3H), 1.13 (s, 3H), 3.50 (dd, *J* = 11.0, 7.5 Hz, 1H), 3.55 (d, *J* = 11.0 Hz, 1H), 3.57 (d, *J* = 11.0, 5.0 Hz, 1H), 3.72 (d, *J* = 11.0 Hz, 1H), 3.91 (dd, *J* = 7.5, 5.0 Hz, 1H), 6.06 (d, *J* = 3.0 Hz, 1H), 6.28 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 16.4, 18.7, 54.2, 54.8, 65.3, 68.1, 75.5, 141.2, 144.0; HRMS (ESI), calcd for $C_9H_{16}O_3Na$ $(M+Na)^+$ 195.0997, found 195.0993.



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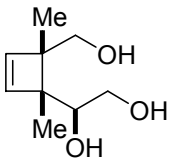


diastereomer of 15

***p*-Bromobenzoate ester 23.** To a solution of **15** (61.6 mg, 358 μmol) and pyridine (57.8 mg, 715 μmol) in CH_2Cl_2 (3.6 ml) was added *p*-bromobenzoyl chloride (157 mg, 715 μmol). The mixture was stirred at room temperature for 4 h, and diluted with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified with flash column chromatography (hexane/$CHCl_3$ 1:1 to 1:2) to give 28.3 mg of **23** (22%). The single crystal was obtained by recrystallization from hexane/Et_2O: colorless crystal; m.p. 104-105 ºC; R_f = 0.17 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{25}_D$ +23.8 (*c* 1.16, $CHCl_3$); IR (film) 3340, 1719, 1272 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.27 (s, 3H), 2.81 (bs, 2H), 3.52 (d, *J* = 12.0 Hz, 1H), 3.99 (d, *J* = 12.0 Hz, 1H), 4.30 (dd, *J* = 8.0, 2.5 Hz, 1H), 4.35 (dd, *J* = 11.0, 8.0 Hz, 1H), 4.40 (dd, *J* = 11.0, 2.5 Hz, 1H), 6.04 (d, *J* = 3.0 Hz, 1H), 6.10 (d, *J* = 3.0 Hz, 1H), 7.59 (m, 2H), 7.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 18.9, 53.96, 54.04, 67.6, 67.7, 73.5, 128.4, 128.7, 131.3, 131.8, 140.2, 141.4, 166.4; HRMS (ESI), calcd for $C_{16}H_{19}BrO_4Na$ $(M+Na)^+$ 377.0364, found 377.0358.

Isopropylidene acetal 16. To a solution of **15** (6.74 g, 39.1 mmol) and dimethoxypropene (6.49 mL, 52.8 mmol) in CH_2Cl_2 (80 mL) was added *p*-TsOH·H_2O (372 mg, 1.96 mmol). The reaction mixture was stirred at room temperature for 30 min and quenched with Et_3N (2.72 mL, 19.6 mmol) and then saturated aqueous sodium bicarbonate. The aqueous layer was extracted with CH_2Cl_2 and Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified with flash column chromatography (hexane/Et_2O 30:1 to 10:1) to give 6.74 g of **16** (81%): yellow oil; R_f = 0.29 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{24}_D$ –3.9 (*c* 0.98, $CHCl_3$); IR (film) 3509, 2987, 1063 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.27 (s, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 3.21 (s, 1H), 3.34 (d, *J* = 12.0 Hz, 1H), 3.81 (dd, *J* = 8.0, 6.5 Hz, 1H), 3.98 (d, *J* = 12.0 Hz, 1H), 4.01 (dd, *J* = 8.0, 6.5 Hz, 1H), 4.43 (dd, *J* = 6.5, 6.5 Hz, 1H), 5.88 (d, *J* = 3.0 Hz, 1H), 6.04 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 19.5, 24.8, 26.0, 51.7, 54.4, 65.9, 67.2, 78.6, 109.5, 139.2, 142.4; HRMS (ESI), calcd for $C_{12}H_{20}O_3Na$ $(M+Na)^+$ 235.1310, found 235.1306.

1,2-diol 17. To a solution of **16** (6.74 g, 31.7 mmol) and benzyl bromide (7.59 mL, 63.4 mmol) in THF (60 mL) and DMF (6 mL) was added NaH (1.60 g, 63.4 mmol). The reaction mixture was stirred at room temperature for 1.5 d and quenched with H_2O. The aqueous layer was extracted twice with Et_2O. The combined organic layer was washed with H_2O twice and brine, dried over $MgSO_4$ and concentrated to give a crude benzyl ether (16.2 g), which was used in the next reaction without further purification.

For analytical sample, the crude mixture was purified with HPLC (YMC-Pack R&D SIL-06, 250x20 mm, UV 254 nm, hexane/EtOAc 10:1, 9.9 mL/min, T_R = 12 min) to give the pure benzyl ether: yellow oil; R_f = 0.61 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{18}_D$ –31.3 (*c* 1.05, $CHCl_3$); IR (film) 2986, 1064 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.19 (s, 3H), 1.31 (s, 3H), 1.41 (s, 3H), 3.51 (d, *J* = 9.5 Hz, 1H), 3.62 (d, *J* = 9.5 Hz, 1H), 3.72 (dd, *J* = 8.0, 7.0 Hz, 1H), 3.89 (dd, *J* = 8.0, 6.5 Hz, 1H), 4.40 (dd, *J*

= 7.0, 6.5 Hz, 1H), 4.53 (s, 2H), 5.89 (d, *J* = 3.0 Hz, 1H), 6.21 (d, *J* = 3.0 Hz, 1H), 7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.3, 19.9, 25.2, 26.5, 52.9, 53.2, 66.6, 73.6, 74.9, 78.4, 109.1, 127.6, 127.7, 128.5, 139.0, 139.1, 143.1; HRMS (ESI), calcd for $C_{19}H_{26}O_3Na$ $(M+Na)^+$ 325.1780, found 325.1774.

A solution of the above benzyl ether in THF (100 mL) and 3 M HCl (20 mL) was stirred for 1 d. The mixture was diluted with Et_2O and the aqueous layer was extracted twice with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified with open column chromatography (hexane/Et_2O 2:1 to 1:3) to give 7.55 g of **17** (91%): colorless oil; R_f = 0.38 (silica gel, 1:1 hexane/EtOAc); $[\alpha]^{17}_D$ –7.7 (*c* 1.09, $CHCl_3$); IR (film) 3440, 2870, 1082 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.22 (s, 3H), 1.77 (s, 1H), 3.36 (d, *J* = 10.0 Hz, 1H), 3.54 (dd, *J* = 11.0, 3.0 Hz, 1H), 3.64 (dd, *J* = 11.0, 8.5 Hz, 1H), 3.84 (d, *J* = 10.0 Hz, 1H), 3.95 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.24 (s, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 5.94 (d, *J* = 3.0 Hz, 1H), 6.02 (d, *J* = 3.0 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.9, 19.3, 52.7, 54.2, 63.8, 73.7, 74.9, 75.6, 127.9, 128.0, 128.5, 137.0, 140.2, 141.2; HRMS (ESI), calcd for $C_{16}H_{22}O_3Na$ $(M+Na)^+$ 285.1467, found 285.1461.

Alcohol 18. A cooled solution (–50 ºC) of **17** (15.7 g, 59.8 mmol) and pyridine (7.74 mL, 95.7 mmol) in CH_2Cl_2 (1.2 L) was added $Pb(OAc)_4$ (42.4 g, 95.7 mmol). The mixture was cooled to –78 ºC and 1.01 M DIBAL in toluene (1.18 L, 1.20 mmol) was added. Then the mixture was allowed to warm to –50 ºC over 30 min and quenched with saturated aqueous Rochelle salt. The aqueous layer was extracted twice with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified with open column chromatography (hexane/EtOAc 8:1 to EtOAc) to give 11.7 g of **18** (84%) along with recovered **17** (1.51 g, 10%): **18**: colorless oil; R_f = 0.37 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{22}_D$ –12.5 (*c* 0.89, $CHCl_3$); IR (film) 3466, 2867, 1068 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.24 (s, 3H), 3.33 (d, *J* = 12.0 Hz, 1H), 3.34 (d, *J* = 9.5 Hz, 1H), 3.51 (s, 1H), 3.75 (d, *J* = 9.5 Hz, 1H), 3.82 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.5 Hz, 1H), 4.61 (d,

J = 12.5 Hz, 1H), 5.96 (d, J = 3.0 Hz, 1H), 6.01 (d, J = 3.0 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 19.6, 51.5, 53.5, 67.8, 73.7, 76.0, 127.9, 127.9, 128.5, 137.3, 140.0, 141.6; HRMS (ESI), calcd for $C_{15}H_{20}O_2Na$ $(M+Na)^+$ 255.1361, found 255.1356.

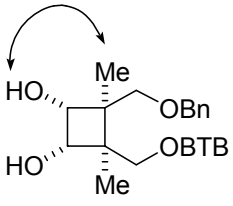
BTB ether 19. A mixture of **18** (19.7 g, 84.8 mmol), 18-crown-6 (4.48 g, 17.0 mmol) and 2,6-bis(trifluoromethyl)benzyl bromide (BTBBr) (41.8 g, 136 mmol) in DMF was cooled to 0 ºC, and then KH (30 wt % dispersion in mineral oil, 25.0 g, 187 mmol) was added. After being warmed to room temperature, the reaction mixture was stirred for 5 h and quenched with MeOH and then H_2O. The aqueous layer was extracted three times with Et_2O. The combined organic layer was washed with H_2O twice and brine, dried over $MgSO_4$ and concentrated. The residue was filtrated through a pad of silica gel to give 2.24 g of recovered **18** (11%) and 42.6 g mixture of **19** and BTBBr, which was used in the next reaction without further purification

For analytical sample, the crude mixture was purified with HPLC (YMC-Pack R&D SIL-06, 250x20 mm, UV 254 nm, hexane/EtOAc 10:1, 9.9 mL/min, T_R = 10 min) to give pure **19**: colorless oil; R_f = 0.62 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{24}_D$ –9.7 (*c* 1.00, $CHCl_3$); IR (film) 1287, 1173, 1135 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.15 (s, 3H), 3.47 (d, J = 9.0 Hz, 1H), 3.49 (d, J = 8.5 Hz, 1H), 3.53 (d, J = 9.0 Hz, 1H), 3.68 (d, J = 8.5 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.52 (d, J = 12.0 Hz, 1H), 4.58 (d, J =11.5 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 6.09 (d, J = 3.0 Hz, 1H), 6.12 (d, J = 3.0 Hz, 1H), 7.30 (m, 5H), 7.56 (t, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.8, 19.2, 51.57, 51.63, 65.2, 73.1, 75.2, 76.7, 123.7 (q, J = 273 Hz, 2C), 127.3, 127.5, 128.2, 128.5, 129.9 (q, J = 5.6 Hz, 2C), 132.0 (q, J = 30.5 Hz, 2C), 135.4, 138.9, 141.1, 141.3; HRMS (ESI), calcd for $C_{24}H_{24}F_6O_2Na$ $(M+Na)^+$ 481.1578, found 481.1575.

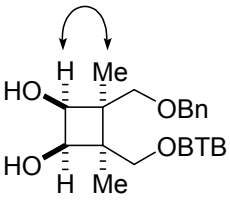
Diol 20. A solution of the above mixture in *t*-BuOMe (200 mL), *t*-BuOH (100 mL) and H_2O (100 mL) was treated with NMO (50 wt % in H_2O, 42.0 mL, 254 mmol) and OsO_4 (39 mM in *t*-BuOH, 44.6

mL, 1.70 mmol), and the mixture was stirred at room temperature for 16 h. Then, the solution was diluted with H_2O, and extracted three times with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified with open column chromatography (hexane/EtOAc 4:1 to 1:1) to give 35.2 g of **20** as a mixture of two diastereomers (84% for 2 steps, **20α**:**20β**=1.0:1.1): **20α**: yellow oil; R_f = 0.14 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{23}_D$ –0.5 (*c* 1.41, $CHCl_3$); IR (film) 3401, 2915 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.02 (s, 6H), 2.48 (s, 2H), 3.42 (s, 2H), 3.48 (d, *J* = 9.0 Hz, 1H), 3.53 (d, *J* = 9.0 Hz, 1H), 4.05 (d, *J* = 6.0 Hz, 1H), 4.07 (d, *J* = 6.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 7.31 (m, 5H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 13.6, 45.6, 45.7, 65.0, 70.19, 70.22, 73.0, 74.8, 76.1, 23.7 (q, *J* = 273 Hz, 2C), 127.42, 127.45, 128.3, 128.6, 129.9 (q, *J* = 5.8 Hz, 2C), 131.9 (q, *J* = 30.5 Hz, 2C), 134.9, 138.5; HRMS (ESI), calcd for $C_{24}H_{26}F_6O_4Na$ $(M+Na)^+$ 515.1633, found 515.1628. **20β**: yellow oil; R_f = 0.21 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{23}_D$ –11.3 (*c* 1.07, $CHCl_3$); IR (film) 3422, 2914 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 3H), 1.09 (s, 3H), 3.20 (d, *J* = 6.5 Hz, 1H), 3.47 (d, *J* = 6.5 Hz, 1H), 3.63 (d, *J* = 9.5 Hz, 1H), 3.71 (d, *J* = 9.0 Hz, 1H), 3.73 (d, *J* = 9.5 Hz, 1H), 3.75 (d, *J* = 9.0 Hz, 1H), 3.89 (dd, *J* = 6.5, 6.5 Hz, 1H), 3.96 (dd, *J* = 6.5, 6.5 Hz, 1H), 4.52 (d, *J* =11.5 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.63 (s, 2H), 7.35 (m, 5H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6, 20.1, 44.0, 45.4, 65.1, 72.5, 74.0, 76.7, 77.0, 77.3, 23.6 (q, *J* = 273 Hz, 2C), 127.76, 127.85, 128.5, 128.8, 130.0 (q, *J* = 5.3 Hz, 2C), 131.9 (q, *J* = 30.5 Hz, 2C) 134.6, 137.7; HRMS (ESI), calcd for $C_{24}H_{26}F_6O_4Na$ $(M+Na)^+$ 515.1633, found 515.1627.

NOE data of diol **20α** and **20β** (500 MHz, $CDCl_3$)



20α

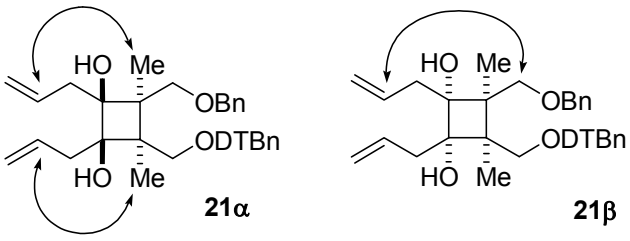


20β

Diene 21. A solution of **20** (1.09 g, 2.21 mmol) and *i*-Pr_2NEt (3.85 mL, 22.1 mmol) in DMSO (2.8 mL) and CH_2Cl_2 (19.6 mL) was cooled to –15 ºC. SO_3·Py (1.76 g, 11.1 mmol) was added, and then the mixture was stirred at –15 ºC for 20 min and cooled to -78 ºC. The reaction mixture was transferred into the allyl magnesium bromide in Et_2O (0.5 M, 35.4 mL, 17.7 mmol) at –78 ºC. The mixture was stirred vigorously at –78 ºC for 10 min and quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 40:1 to 10:1) to give 992 mg of **21** as a mixture of two diastereomers (78% for 2 steps, **21α**:**21β**=2.7:1): **21α**: yellow oil; R_f = 0.55 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{24}_D$ –6.5 (*c* 0.93, $CHCl_3$); IR (film) 3468, 2922 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.09 (s, 3H), 2.26 (dd, *J* = 14.5, 7.0 Hz, 1H), 2.33 (dd, *J* = 14.5, 6.5 Hz, 1H), 2.39 (dd, *J* = 14.5, 7.0 Hz, 1H), 2.45 (dd, *J* = 14.5, 6.5 Hz, 1H), 3.64 (d, *J* = 9.0 Hz, 1H), 3.71 (d, *J* = 9.5 Hz, 1H), 3.73 (d, *J* = 9.5 Hz, 1H), 3.77 (d, *J* = 9.0 Hz, 1H), 3.80 (s, 1H), 3.97 (s, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.94 (d, *J* = 10.0 Hz, 1H), 5.02 (d, *J* = 17.0 Hz, 1H), 5.05 (d, *J* = 10.0 Hz, 1H), 5.08 (d, *J* = 17.0 Hz, 1H), 5.78 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.91 (dddd, *J* = 17.0, 10.0, 6.5, 6.5 Hz, 1H), 7.32 (m, 5H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.1, 17.1, 38.2, 38.8, 46.5, 47.2, 65.0, 73.3, 73.7, 74.8, 77.5, 77.8, 117.5, 117.5, 123.7 (q, *J* = 273 Hz, 2C), 127.6, 127.6, 128.3, 128.7, 130.0 (q, *J* = 5.3 Hz, 2C), 132.0 (q, *J* = 30.0 Hz, 2C), 134.4, 134.6, 134.8, 138.3; HRMS (ESI), calcd for $C_{30}H_{34}F_6O_4Na$ $(M+Na)^+$ 595.2259, found 595.2251. **21β**: yellow oil; R_f = 0.45 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{24}_D$ –4.8 (*c* 1.16, $CHCl_3$); IR (film) 3526, 2910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.07 (s, 3H), 2.39 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.41 (dd, *J* = 14.5, 7.5 Hz, 1H), 2.58 (dd, *J* = 14.5, 6.0 Hz, 1H), 2.62 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.95 (s, 2H), 3.54 (d, *J* = 10.0 Hz, 1H), 3.57 (d, *J* = 9.0 Hz, 1H), 3.58 (d, *J* = 10.0 Hz, 1H), 3.68 (d, *J* = 9.0 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 12.0 Hz,

1H), 4.60 (d, J = 12.0 Hz, 1H), 5.05 (d, J = 14.0 Hz, 1H), 5.07 (d, J = 9.5 Hz, 1H), 5.07 (d, J = 9.0 Hz, 1H), 5.10 (d, J = 14.0 Hz, 1H), 5.84 (dddd, J = 14.0, 9.5, 7.5, 6.0 Hz, 1H), 5.94 (dddd, J = 14.0, 9.0, 7.5, 6.5 Hz, 1H), 7.34 (m, 5H), 7.57 (t, J = 7.5 Hz, 1H), 7.90 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.40, 15.45, 37.6, 38.2, 47.9, 48.2, 65.1, 73.3, 73.3, 74.6, 77.3, 77.7, 118.4, 118.6, 123.7 (q, J = 273 Hz, 2C), 127.4, 127.6, 128.3, 128.6, 130.0 (q, J = 5.3 Hz, 2C), 132.0 (q, J = 30.5 Hz, 2C), 134.77, 134.85, 134.9, 138.5; HRMS (ESI), calcd for $C_{30}H_{34}F_6O_4Na$ $(M+Na)^+$ 595.2259, found 595.2252.

NOE data of **21α** and **21β** (500 MHz, $CDCl_3$)



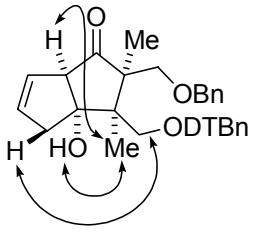
Diketone 6. To a solution of **21** (992 mg, 1.73 mmol) in dichloromethane (86.5 mL) was added $(PCy_3)_2Cl_2Ru$=CHPh (142 mg, 173 μmol), and the resultant mixture was heated to reflux for 17 h. After being cooled to room temperature, the solution was treated with $Pb(OAc)_4$ (923 mg, 2.00 mmol). Then, the mixture was filtrated through a pad of silica gel to give 910 mg of **6** (97%): gray crystal; m.p. 114-115 ºC; R_f = 0.43 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{24}_D$ –22.3 (*c* 1.24, $CHCl_3$); IR (film) 1714, 1693 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.29 (s, 3H), 2.86 (m, 1H), 3.03 (m, 1H), 3.20 (d, J = 15.0 Hz, 1H), 3.20 (d, J = 15.0 Hz, 1H), 3.42 (d, J = 8.0 Hz, 1H), 3.48 (d, J = 9.0 Hz, 1H), 4.05 (d, J = 8.0 Hz, 1H), 4.15 (d, J = 9.0 Hz, 1H), 4.42 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 11.0 Hz, 1H), 4.62 (d, J = 11.0 Hz, 1H), 5.66 (m, 2H), 7.30 (m, 5H), 7.55 (t, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6, 16.3, 39.9, 41.9, 56.0, 56.2, 65.2, 76.7, 77.0, 77.3, 23.6 (q, J = 273 Hz, 2C), 125.0, 125.1, 127.3, 127.6, 128.3, 128.8, 129.5 (q, J = 5.3 Hz, 2C), 132.0 (q, J = 30.5 Hz, 2C), 134.3, 138.0, 210.0, 211.7; HRMS (ESI), calcd for $C_{28}H_{28}F_6O_4Na$ $(M+Na)^+$

565.1789, found 565.1784.

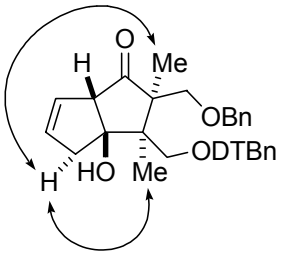
Aldol product 8. The solution of fleshly prepared $NaN(TMS)_2$ (5.47 g, 28.3 mmol) in THF (52.4 mL) was transferred to the solution of **6** (5.12 g, 9.44 mmol) in THF (262 mL) at –100 ºC over 4 min. The reaction mixture was stirred at –100 ºC for 10 min and quenched with pH 7 phosphate buffer. The aqueous layer was extracted twice with Et_2O. The organic layer was washed with saturated aqueous ammonium chloride and brine, dried over $MgSO_4$ and concentrated. The residue was filtrated through a pad of silica gel to give a mixture of four diastereomers. The mixture was purified with MPLC (YAMAZEN ULTRA PACK, 80x300 mm, hexane/EtOAc 18:1 to 6:1, 150 mL/min) to give a mixture of **8** and **27** (3.98 g, 78%, **8**:**27**=27:1), 768 mg of **26** (15%) and 225 mg of **25** (4%): **8**: yellow oil; R_f = 0.30 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{27}_D$ –169.5 (*c* 0.975, $CHCl_3$); IR (film) 3423, 2926, 1736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.17 (s, 3H), 2.25 (s, 1H), 2.44 (d, *J* = 19.0 Hz, 1H), 2.96 (dd, *J* = 19.0, 2.0 Hz, 1H), 3.02 (d, *J* = 9.5 Hz, 1H), 3.16 (s, 1H), 3.37 (d, *J* = 9.5 Hz, 1H), 3.54 (d, *J* = 9.0 Hz, 1H), 4.11 (d, *J* = 9.0 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.63 (d , *J* = 11.0 Hz, 1H), 4.75 (d, *J* = 11.0 Hz, 1H), 5.61 (m, 2H), 7.33 (m, 5H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.2, 19.5, 47.7, 50.2, 60.2, 65.3, 65.8, 72.8, 73.4, 76.0, 86.8, 123.7 (q, *J* = 273 Hz, 2C), 126.8, 127.9, 128.0, 128.4, 129.1, 130.6 (q, *J* = 5.6 Hz, 2C), 131.7, 132.0 (q, *J* = 30.5 Hz, 2C), 134.3, 137.6, 215.2; HRMS (ESI), calcd for $C_{28}H_{28}F_6O_4Na$ $(M+Na)^+$ 565.1789, found 565.1782. **25**: yellow oil; R_f = 0.38 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{27}_D$ +94.7 (*c* 0.99, $CHCl_3$); IR (film) 3434, 2927, 1737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.04 (s, 3H), 2.48 (ddd, *J* = 18.0, 3.5, 2.0 Hz, 1H), 2.97 (ddd, *J* = 18.0, 4.5, 2.5 Hz, 1H), 3.09 (m 1H), 3.55 (d, *J* = 9.5 Hz, 1H), 3.57 (d, *J* = 9.5 Hz, 1H), 3.61 (d, *J* = 9.5 Hz, 1H), 3.76 (s, 1H), 3.80 (d, *J* = 9.5 Hz, 1H), 4.49 (d, *J* = 12.5 Hz, 1H), 4.50 (s, 2H), 4.54 (d, *J* = 12.5 Hz, 1H), 5.63 (m, 1H), 5.67 (m, 1H), 7.35 (m, 5H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.0, 18.7, 44.9, 50.0, 56.4, 64.8, 68.9, 73.8, 74.0, 74.5, 86.5, 123.6 (q, *J* = 273 Hz, 2C),

127.9, 128.03, 128.06, 128.5, 129.0, 130.1 (q, J = 5.3 Hz, 2C), 131.1, 131.9 (q, J = 30.0 Hz, 2C), 134.0, 137.2, 217.9; HRMS (ESI), calcd for $C_{28}H_{28}F_6O_4Na$ $(M+Na)^+$ 565.1789, found 565.1782. **26**: yellow oil; R_f = 0.25 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{27}_D$ +140.5 (*c* 1.13, $CHCl_3$); IR (film) 3503, 2916, 1736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.16 (s, 3H), 2.45 (s, 1H), 2.52 (d, J = 18.5 Hz, 1H), 3.18 (dd, J = 18.5, 2.0 Hz, 1H), 3.22 (d, J = 9.5 Hz, 1H), 3.32 (d, J = 2.5 Hz, 1H), 3.36 (d, J = 9.5 Hz, 1H), 3.56 (d , J = 9.5 Hz, 1H), 3.87 (d, J = 9.5 Hz, 1H), 4.38 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 11.0 Hz, 1H), 4.55 (d, J = 11.0 Hz, 1H), 5.68 (dd, J = 5.5, 2.5 Hz, 1H), 5.71 (dd, J = 5.5, 2.0 Hz, 1H), 7.29 (m, 5H), 7.59 (t, J = 7.5 Hz, 1H), 7.91 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.7, 18.4, 47.7, 50.3, 59.1, 65.1, 66.4, 73.5, 74.5, 74.7, 87.0, 123.6 (q, J = 273 Hz, 2C), 126.6, 127.64, 127.69, 128.4, 128.8, 130.0, (q, J = 5.3 Hz, 2C), 131.0, 132.0 (q, J = 30.5 Hz, 2C), 134.4, 137.9, 215.4; HRMS (ESI), calcd for $C_{28}H_{28}F_6O_4Na$ $(M+Na)^+$ 565.1789, found 565.1781.

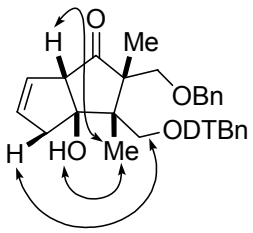
NOE data of **8**, **25** and **26**



8 (500 MHz, $CDCl_3$)

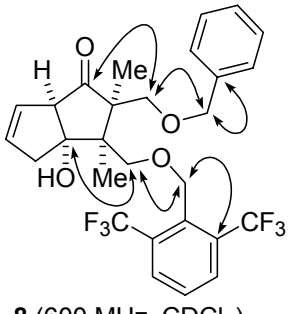


25 (600 MHz, $CDCl_3$)

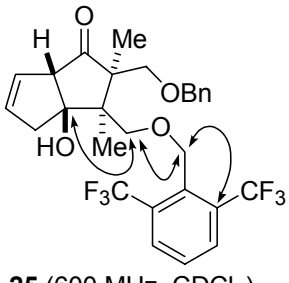


26 (500 MHz, $CDCl_3$)

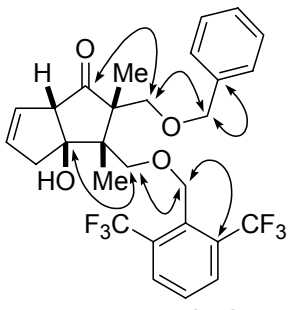
HMBC correlation of **8**, **25** and **26**



8 (600 MHz, $CDCl_3$)



25 (600 MHz, $CDCl_3$)



26 (600 MHz, $CDCl_3$)

Allylic alcohol 28. A solution of **8** (4.02 g, 7.41 mmol) in CH_2Cl_2 (148 mL) was treated with *m*CPBA

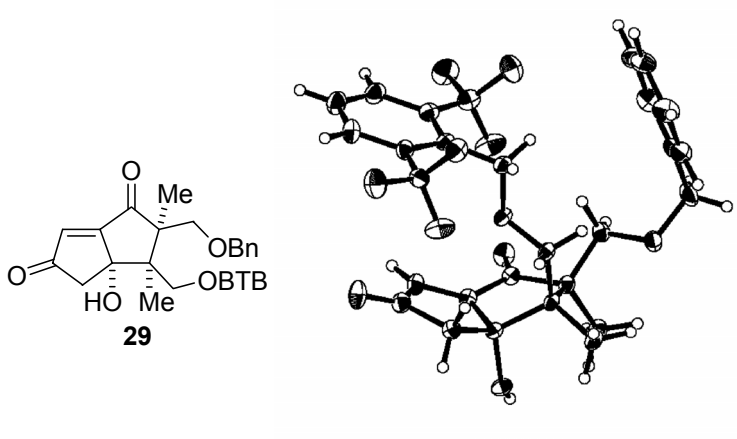
(77 wt %, 4.98 g, 22.2 mmol). The reaction mixture was stirred at room temperature for 3 h, and then quenched with saturated aqueous sodium thiosulfate. The aqueous layer was extracted twice with Et_2O. The organic layer was washed with saturated aqueous sodium bicarbonate twice and brine, dried over $MgSO_4$, and concentrated to give a crude epoxide, which was used in the next reaction without further purification.

The above epoxide was treated with florisil (40.2 g) in CH_2Cl_2 (148 mL). The mixture was stirred at room temperature for 11 h and filtrated through a pad of silica gel to give 3.09 g of **28** (75%): colorless amorphous solid; R_f = 0.31 (silica gel, 1:1 hexane/EtOAc); $[\alpha]^{27}_D$ +28.3 (*c* 1.06, $CHCl_3$); IR (film) 3401, 2915, 1714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.48 (s, 3H), 1.70 (d, *J* = 14.0 Hz, 1H), 2.79 (s, 1H), 2.39 (s, 1H), 2.47 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.46 (d, *J* = 9.0 Hz, 1H), 3.46 (d, *J* = 10.0 Hz, 1H), 3.56 (d, *J* = 10.0 Hz, 1H), 3.67 (d, *J* = 9.0 Hz, 1H), 4.36 (d, *J* = 11.0 Hz, 1H), 4.42 (d, *J* = 11.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.77 (d, *J* = 6.0 Hz, 1H), 6.34 (s,1H), 7.29 (m, 1H), 7.36 (m, 4H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.5, 21.3, 43.2, 48.3, 59.8, 64.6, 73.0, 73.4, 75.6, 79.4, 88.2, 123.5 (q, *J* = 274 Hz, 2C), 127.5, 127.6, 128.3, 128.9, 130.1 (q, *J* = 5.8 Hz, 2C), 131.7 (q, *J* = 30.1 Hz, 2C), 134.0, 134.3, 138.5, 152.8, 204.3; HRMS (ESI), calcd for $C_{28}H_{28}F_6O_5Na$ $(M+Na)^+$ 581.1739, found 581.1734.

Enedione 29. A solution of **28** (2.13 g, 3.83 mmol) in DMSO (25.5 mL) was treated with IBX (3.22 g, 11.5 mmol), and the mixture was stirred at room temperature for 1 h. Then, the solution was diluted with H_2O and Et_2O, filtrated through Celite. The aqueous layer was extracted five times with diethyl ether. The combined organic layer was washed with sodium bicarbonate and brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 10:1 to 3:1) to give 1.96 g of **29** (92%). The single crystal was obtained by recrystallization from hexane/EtOAc: yellow crystal; m.p. 137-138 ºC; R_f = 0.22 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{24}_D$ +51.3 (*c* 1.07, $CHCl_3$); IR (film) 3483, 2876, 1719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.19 (s, 3H),

1.54 (s, 3H), 2.31 (d, J = 18.0 Hz, 1H), 2.84 (d, J = 18.0 Hz, 1H), 3.47 (d, J = 10.0 Hz, 1H), 3.52 (d, J = 9.5 Hz, 1H), 3.63 (d, J = 9.5 Hz, 1H), 3.65 (d, J = 10.0 Hz, 1H), 4.21 (d, J = 11.5 Hz, 1H), 4.34 (d, J = 11.5 Hz, 1H), 4.42 (d, J = 12.0 Hz, 1H), 4.60 (d, J = 12.0 Hz, 1H), 5.92 (s, 1H), 7.30 (m, 1H), 7.37 (m, 5H), 7.55 (t, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 21.4, 47.1, 49.2, 56.6, 64.3, 72.7, 73.6, 75.1, 82.7, 123.3 (q, J = 273 Hz, 2C), 127.7, 127.9, 128.1, 128.4, 129.1, 130.4 (q, J = 5.8 Hz, 2C), 131.5 (q, J = 30.5 Hz, 2C), 133.3, 138.1, 171.4, 204.4, 208.1; HRMS (ESI), calcd for $C_{28}H_{26}F_6O_5Na$ $(M+Na)^+$ 579.1582, found 579.1576.

X-ray crystallographic analysis of **29**



29

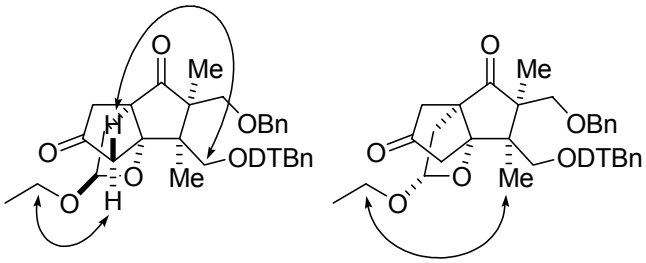
α-Bromoacetal 30. To a solution of bromine (10.9 mL, 212 mmol) in CH_2Cl_2 (70.7 mL) at –78 ºC was added ethyl vinyl ether (21.0 mL, 221 mmol) dropwise. The resultant mixture was stirred at –78 ºC for 15 min, warmed to room temperature over 5 min, and then recooled to –78 ºC. This mixture was added to a solution of **29** (5.88 g, 10.6 mmol) and *N,N*-dimethylaniline (53.7 mL, 424 mmol) in CH_2Cl_2 (212 mL). The mixture was allowed to warm to 0 ºC, and stirred at 0 ºC for 10 h and at room temperature for 14 h. Then, the solution was diluted with 1 M HCl. The aqueous layer was extracted twice with Et_2O. The organic layer was washed with 1 M HCl three times and brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 8:1 to 2:1) to give 5.46 g of an inseparable diastereomeric mixture of **30** (73%, dr=4.4:1) along with recovered **29** (1.23 g, 21%): **major isomer**: yellow oil; R_f = 0.48 (silica gel, 3:1

hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.0 Hz, 3H), 1.18 (s, 3H). 1.56 (s, 3H), 2.46 (d, *J* = 19.0 Hz, 1H), 2.86 (d, *J* = 19.0 Hz, 1H), 2.99 (dq, *J* = 9.0, 7.0 Hz, 1H), 3.22 (dq, *J* = 9.0, 7.0 Hz, 1H), 3.21 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.27 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.49 (d, *J* = 10.5 Hz, 1H), 3.51 (d, *J* = 9.0 Hz, 1H), 3.61 (d, *J* = 10.5 Hz, 1H), 3.61 (d, *J* = 9.0 Hz, 1H), 4.10 (dd, *J* = 7.0, 3.0 Hz, 1H), 4.16 (d, *J* = 11.0 Hz, 1H), 4.30 (d, *J* = 11.0 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 5.89 (s, 1H), 7.33 (m, 5H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 2H); HRMS (ESI), calcd for $C_{32}H_{33}BrF_6O_6Na$ $(M+Na)^+$ 729.1262, found 729.1256.

Cyclized product 31 and 32. To a solution of **30** (4.46 g, 6.3 mmol) and Bu_3SnH (16.9 mL, 63.0 mmol) in toluene (315 mL) was added AIBN (3.11 g, 18.9 mmol). The mixture was heated to 85 ºC. After being stirred for 1 h at 85 ºC, the mixture was concentrated, and purified with flash column chromatography (hexane/EtOAc 10:1 to 2:1) to give 2.91 g of **31** (73%) and 690 mg of **32** (17%). **31**: colorless amorphous solid; R_f = 0.38 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{25}_D$ –25.6 (*c* 1.00, $CHCl_3$); IR (film) 2929, 2877, 1743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (t, *J* = 7.0 Hz, 3H), 1.10 (s, 3H), 1.25 (s, 3H), 2.13 (d, *J* = 14.5 Hz, 1H), 2.33 (s, 2H), 2.37 (dd, *J* = 14.5, 5.5 Hz, 1H), 2.45 (d, *J* = 19.5 Hz, 1H), 2.97 (d, *J* = 19.5 Hz, 1H), 3.55 (dq, *J* = 9.5, 7.0 Hz, 1H), 3.38 (d, *J* = 9.5 Hz, 1H), 3.45 (d, *J* = 10.0 Hz, 1H), 3.47 (d, *J* = 10.0 Hz, 1H), 3.47 (d, *J* = 9.5 Hz, 1H), 3.66 (dq, *J* = 9.5, 7.0 Hz, 1H), 4.23 (d, *J* = 11.5 Hz, 1H), 4.27 (d, *J* = 12.0 Hz, 1H), 4.29 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 5.19 (d, *J* = 5.5 Hz, 1H), 7.32 (m, 5H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.88 (d, , *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 15.9, 20.7, 47.8, 48.6, 48.8, 49.4, 55.8, 61.4, 62.6, 64.4, 73.49, 73.54, 74.9, 97.8, 105.2, 123.4 (q, *J* = 273 Hz, 2C), 127.9, 128.2, 128.5, 129.2, 130.0 (q, *J* = 5.6 Hz, 2C), 132.0 (q, *J* = 30.0 Hz, 2C), 133.0, 137.5, 214.9, 220.3; HRMS (ESI), calcd for $C_{32}H_{34}F_6O_6Na$ $(M+Na)^+$ 651.2157, found 651.2153. **32**: colorless amorphous solid; R_f = 0.24 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{25}_D$ +33.4 (*c* 1.22, $CHCl_3$); IR (film) 2930, 2879, 1743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (s,3H), 1.19 (t, *J* = 7.0 Hz, 3H), 1.46 (s, 3H), 2.11 (d, *J* = 19.5 Hz, 1H), 2.22 (d, *J* = 19.5 Hz, 1H), 2.22 (dd, *J* =

15.0, 6.5 Hz, 1H), 2.25 (dd, *J* = 15.0, 6.5 Hz, 1H), 2.33 (d, *J* = 19.5 Hz, 1H), 2.98 (d, *J* = 19.5 Hz, 1H), 3.42 (d, *J* = 9.0 Hz, 1H), 3.44 (d, *J* = 9.5 Hz, 1H), 3.49 (d, *J* = 9.5 Hz, 1H), 3.49 (d, *J* = 9.0 Hz, 1H), 3.52 (dq, *J* = 9.5, 7.0 Hz, 1H), 3.79 (dq, *J* = 9.5, 7.0 Hz, 1H), 4.21 (d, *J* = 12.0 Hz, 1H), 4.24 (d, *J* = 11.5 Hz, 1H), 4.26 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 5.18 (dd, *J* = 6.5, 6.5 Hz, 1H), 7.32 (m, 5H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.3, 16.0, 20.9, 46.6, 47.7, 49.0, 49.2, 55.4, 60.2, 64.3, 65.5, 73.4, 73.5, 74.9, 95.3, 104.5, 123.4 (q, *J* = 273 Hz, 2C), 127.8, 128.1, 128.4, 129.2, 130.0 (q, *J* = 5.6 Hz, 2C), 132.0 (q, *J* = 30.1 Hz, 2C), 132.7, 137.8, 213.8, 220.1; HRMS (ESI), calcd for $C_{32}H_{34}F_6O_6Na$ $(M+Na)^+$ 651.2157, found 651.2154.

NOE Data of **31** and **32** (500 MHz, $CDCl_3$)



31 **32**

Isomerization of 32 to 31. A solution of **32** (1.07 g, 1.70 mmol) and EtOTMS (2.66 mL, 17.0 mmol) in CH_2Cl_2 (42.5 mL) was treated with $BF_3{\cdot}Et_2O$ (1.08 mL, 8.50 mmol), and the mixture was heated to 40 °C for 14 h. The reaction mixture was stirred at room temperature for 1 d, and quenched with *i*-Pr_2NEt (2.96 mL, 17.0 mmol) and then saturated aqueous sodium bicarbonate, and extracted twice with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 10:1 to 7:1) to give 767 mg of **31** (72%).

Enone 34. A solution of **31** (89.0 mg, 142 μmol) in CH_2Cl_2 (7 mL) was cooled to –20 ºC and treated with Et_3N (317 μl, 2.27 mmol) and TMSOTf (219 μl, 1.13 mmol). The reaction mixture was stirred

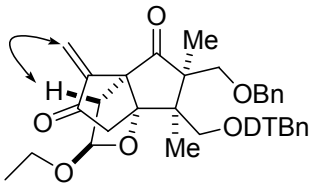
for 2 h at the same temperature, quenched with pH 7 phosphate buffer, and extracted twice with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to give the silyl enol ether **33**, which was used directly in the next reaction

A solution of the above **33** in CH_3CN (7.0 mL) was treated with $Me_2NCH_2^+I^-$ (210 mg, 1.14 mmol). The mixture was stirred at room temperature for 17 h quenched with 0.5 M HCl. Potassium carbonate was introduced to basify the mixture. The aqueous layer was extracted three times with EtOAc. The organic layer was washed with brine and concentrated to give a mixture of the β-amino ketone and **34**, which was used directly in the next reaction.

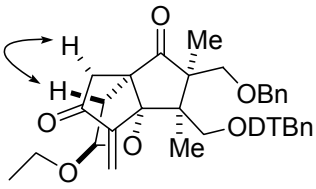
A solution of the above mixture in CH_2Cl_2 (5.0 mL) was treated with *m*CPBA (77 wt %, 47.7 mg, 213 μmol), and the mixture was stirred at room temperature for 1 h. Then, the reaction was quenched with saturated aqueous thiosulfate. The aqueous layer was extracted twice with Et_2O. The organic layer was washed with aqueous sodium bicarbonate three times and brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 10:1 to 4:1) to give 61.4 mg of **34** (64% for 3 steps), along with 3.8 mg of regioisomer of **34** (6% for 3 steps): **34**: colorless amorphous solid; R_f = 0.46 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{27}_D$ –37.1 (*c* 1.24, $CHCl_3$); IR (film) 2929, 2877, 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, *J* = 7.5 Hz, 3H), 1.10 (s, 3H), 1.27 (s, 3H), 2.18 (d, *J* = 14.0 Hz, 1H), 2.49 (d, *J* = 19.5 Hz, 1H), 2.51 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.02 (d, *J* = 19.5 Hz, 1H), 3.33 (dq, *J* = 10.0, 7.5 Hz, 1H), 3.34 (d, *J* = 10.0 Hz, 1H), 3.41 (d, *J* = 10.0 Hz, 1H), 3.44 (d, *J* = 10.0 Hz, 1H), 3.45 (d, *J* = 10.0 Hz, 1H), 3.64 (dq, *J* = 10.0, 7.5 Hz, 1H), 4.14 (d, *J* = 12.0 Hz, 1H), 4.20 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 12.5 Hz, 1H), 4.46 (d, *J* = 12.5 Hz, 1H), 5.18 (d, *J* = 5.5 Hz, 1H), 5.21 (s, 1H), 5.34 (s, 1H), 7.32 (m, 5H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 15.6, 20.8, 46.4, 49.4, 50.1, 56.1, 62.6, 64.2, 65.1, 73.1, 73.5, 74.1, 95.0, 105.1, 116.5, 123.4 (q, *J* = 274 Hz, 2C), 127.8, 128.2, 128.4, 128.9, 129.7 (q, *J* = 5.3 Hz, 2C), 132.0 (q, *J* = 30.5 Hz, 2C), 132.7, 137.5, 147.6, 203.1, 216.6; HRMS (ESI), calcd for $C_{33}H_{34}F_6O_6Na$ $(M+Na)^+$ 663.2157, found 663.2154. **regioisomer of 34**: colorless amorphous solid;

R_f = 0.36 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{28}_D$ –11.7 (*c* 1.06, $CHCl_3$); IR (film) 2930, 2878, 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.21 (s, 3H), 1.39 (s, 3H), 2.06 (d, *J* = 13.5 Hz, 1H), 2.21 (d, *J* = 19.5 Hz, 1H), 2.26 (d, *J* = 19.5 Hz, 1H), 2.35 (dd, *J* = 13.5, 5.0 Hz, 1H), 3.15 (dq, *J* = 9.0, 7.0 Hz, 1H), 3.28 (d, *J* = 9.5 Hz, 1H), 3.33 (d, *J* = 9.5 Hz, 1H), 3.37 (dq, *J* = 9.0, 7.0 Hz, 1H), 3.42 (d, *J* = 9.5 Hz, 1H), 3.47 (d, *J* = 9.5 Hz, 1H), 4.08 (d, *J* = 12.0 Hz, 1H), 4.16 (d, *J* = 12.0 Hz, 1H), 4.21 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 5.15 (d, *J* = 5.0 Hz, 1H), 5.46 (d, *J* = 1.0 Hz, 1H), 5.95 (d, *J* = 1.0 Hz, 1H), 7.40 (m, 5H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.2, 21.6, 46.6, 49.4, 49.5, 54.6, 58.3, 61.1, 64.3, 72.6, 73.5, 75.0, 96.5, 104.0, 117.4, 123.3 (q, *J* = 274 Hz, 2C), 127.7, 128.0, 128.4, 129.2, 130.0 (q, *J* = 5.6 Hz, 2C), 131.9 (q, *J* = 30.6 Hz, 2C), 132.5, 138.0, 147.9, 203.4, 218.8; HRMS (ESI), calcd for $C_{33}H_{34}F_6O_6Na$ $(M+Na)^+$ 663.2157, found 663.2153.

NOE data of **34** and its regioisomer (500 MHz, $CDCl_3$)



34



regioisomer of **34**

γ-lactone 35. To a solution of **34** (28.5 mg, 44.5 μmol) and *m*CPBA (23.0 mg, 133 μmol) in CH_2Cl_2 was added $BF_3{\cdot}Et_2O$ (11.3 μL, 89.0 μmol). The mixture was stirred at room temperature for 10 min and quenched with saturated aqueous thiosulfate. The aqueous layer was extracted twice with Et_2O. The organic layer was washed with aqueous sodium bicarbonate three times and brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 3:1 to 2:1) to give 27.4 mg of **35** (100%): colorless amorphous solid; R_f = 0.18 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{29}_D$ –4.5 (*c* 1.10, $CHCl_3$); IR (film) 2926, 1787, 1738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.18 (s, 3H), 2.48 (d, *J* = 20.0 Hz, 1H), 2.69 (d, *J* = 19.5 Hz, 1H), 3.03 (d,

J = 19.5 Hz, 1H), 3.27 (d, J = 20.0 Hz, 1H), 3.35 (d, J = 10.0 Hz, 1H), 3.46 (d, J = 10.0 Hz, 1H), 3.47 (s, 2H), 4.16 (d, J = 11.0 Hz, 1H), 4.21 (d, J = 11.0 Hz, 1H), 4.26 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 5.39 (s, 1H), 5.46 (s, 1H), 7.32 (m, 5H), 7.60 (t, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.5, 19.4, 29.7, 42.8, 45.7, 50.4, 61.0, 64.3, 72.9, 73.5, 73.6, 94.9, 119.0, 123.4 (q, J = 273 Hz, 2C), 128.1, 128.5, 128.6, 129.2, 129.8 (q, J = 5.3 Hz, 2C), 132.1 (q, J = 30.0 Hz, 2C), 132.3, 136.9, 145.9, 173.7, 199.6, 215.1; HRMS (ESI), calcd for $C_{31}H_{28}F_6O_6Na$ $(M+Na)^+$ 633.1688, found 633.1684.

Enol triflate 36. A solution of **35** (27.4 mg, 44.9 μmol), Commins reagent (52.7 mg, 134 μmol) and MS4A in THF (2.2 mL) was cooled to –78 ºC and treated with L-Selectride (1.02 M in THF, 175 μl, 179 μmol). The resultant solution was stirred at the same temperature for 40 min. Then, the reaction mixture was quenched with H_2O, and extracted twice with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 15:1 to 5:1) to give 24.3 mg of **36** (73%): colorless amorphous solid; R_f = 0.43 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{27}_D$ –100.0 (*c* 1.22, $CHCl_3$); IR (film) 2927, 1788, 1744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.11 (s, 3H), 1.58 (m, 3H), 2.60 (d, J = 19.0 Hz, 1H), 2.67 (d, J = 19.0 Hz, 1H), 2.85 (dq, J = 18.0, 2.0 Hz, 1H), 3.38 (m, 1H), 3.38 (d, J = 9.5 Hz, 1H), 3.44 (d, J = 9.5 Hz, 1H), 3.56 (d, J = 9.0 Hz, 1H), 3.67 (d, J = 9.0 Hz, 1H), 4.38 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 10.5 Hz, 1H), 4.51 (d, J = 10.5 Hz, 1H), 7.33 (m, 5H), 7.61 (t, J = 8.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.8, 17.8, 18.1, 36.1, 40.5, 50.3, 58.6, 64.5, 64.9, 72.8, 73.4, 73.5, 94.1, 118.3 (q, J = 319 Hz, 2C), 123.6 (q, J = 273 Hz, 2C), 127.5, 128.10, 128.11, 128.5, 129.1, 130.0 (q, J = 5.8 Hz, 2C), 131.9 (q, J = 30.5 Hz, 2C), 133.7, 136.9, 141.4, 173.7, 213.4; HRMS (ESI), calcd for $C_{32}H_{29}F_9O_8SNa$ $(M+Na)^+$ 767.1337, found 767.1335.

Olefin 37. A solution of **36** (24.3 mg, 32.6 μmol) and tributylamine (97.5 μL, 391 μmol) in DMF

(2.2 mL) was degassed using the freeze-pump-thaw technique three times. To this mixture were added PPh_3 (34.2 mg, 130 μmol) and $Pd(OAc)_2$ (14.6 mg, 65.2 μmol) and then formic acid (12.3μL, 326 μmol) in DMF (1.0 mL), which was separately degassed using the freeze-pump-thaw technique three times beforehand. The mixture was stirred at 40 ºC for 2 h, and then diluted with H_2O. The aqueous solution was extracted twice with EtOAc. The organic layer was washed with H_2O two times and brine, dried over $MgSO_4$, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 10:1 to 5:1) to give 17.6 mg of **37** (92%): colorless amorphous solid; R_f = 0.32 (silica gel, 3:1 hexane/EtOAc); $[\alpha]^{27}_D$ –180.2 (*c* 1.16, $CHCl_3$); IR (film) 2939, 1777, 1742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.11 (s, 3H), 1.63 (ddd, *J* = 2.5, 2.5, 2.5 Hz, 3H), 2.54 (d, *J* = 18.5 Hz, 1H), 2.63 (d, *J* = 17.5 Hz, 1H), 2.65 (ddq, *J* = 19.0, 2.5, 2.5 Hz, 1H), 3.00 (ddq, *J* = 19.0, 2.5, 2.5 Hz, 1H), 3.31 (d, *J* = 8.5 Hz, 1H), 3.38 (d, *J* = 8.5 Hz, 1H), 3.64 (d, *J* = 9.0 Hz, 1H), 3.70 (d, *J* = 9.0 Hz, 1H), 4.37 (d, *J* = 12.5 Hz, 1H), 4.39 (d, *J* = 12.5 Hz, 1H), 4.60 (d, *J* = 11.0 Hz, 1H), 4.63 (d, *J* = 11.0 Hz, 1H), 5.12 (ddq, *J* = 2.5, 2.5, 2.5 Hz, 1H), 7.24 (m, 2H), 7.33 (m, 3H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.7, 16.6, 18.3, 35.5, 42.5, 49.9, 60.1, 65.2, 69.2, 72.9, 73.0, 73.4, 98.7, 123.6 (q, *J* = 273 Hz, 2C), 126.0, 127.8, 127.9, 128.3, 128.9, 130.0 (q, *J* = 5.3 Hz, 2C), 132.0 (q, *J* = 30.5 Hz, 2C), 134.2, 137.2, 138.1, 175.2, 213.4; HRMS (ESI), calcd for $C_{31}H_{30}F_6O_5Na$ $(M+Na)^+$ 619.1895, found 619.1888.

Bis-γ-lactone 41. To a solution of **37** (70.9 mg, 119 μmol) in THF (5.0 mL) and EtOH (1.0 mL) at –78 ºC was introduced liquid ammonia (12 mL). Then, sodium (73.8 mg, 3.21 mmol) was added to this solution, and the mixture was stirred at –78 °C for 1.5 h. The reaction mixture was quenched with ammonium chloride (859 mg, 16.1 mmol), stirred at –78 ºC for 40 min and allowed to warm to room temperature. After liquid ammonia was removed, the resultant solution was filtrated through Celite and a pad of florisil to give 26.7 mg of lactone **39** and lactol **40** (**39**:**40** = 1.0:1.4).

A solution of the above mixtures in toluene (6.0 mL) was treated with 50% Ag_2CO_3 on Celite (1.34 g,

2.27 mmol) and heated to 130 ºC. The mixture was stirred at the same temperature for 4 h. The suspension was filtrated through Celite, and concentrated. The residue was purified with flash column chromatography (hexane/EtOAc 2:1 to 1.5:1) to give 13.5 mg of **41** (41% for 2 steps): colorless crystal; m.p. 166-169 ºC; R_f = 0.43 (silica gel, 1:1 hexane/EtOAc); $[\alpha]^{25}_D$ –128.4 (*c* 0.75, CH_3OH); IR (film) 3467, 2925, 1770 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.16 (s, 3H), 1.20 (d, *J* = 1.0 Hz, 3H), 1.80 (ddd, *J* = 2.5, 2.0, 1.5 Hz, 3H), 2.37 (ddq, *J* = 18.5, 2.5, 2.5 Hz, 1H), 2.58 (ddq, *J* = 18.5, 2.0, 2.0 Hz, 1H), 2.78 (d, *J* = 19.0 Hz, 1H), 2.88 (d, *J* = 19.0 Hz, 1H), 3.98 (d, *J* = 8.5 Hz, 1H), 4.09 (s, 1H), 4.17 (dd, *J* = 8.5, 1.0 Hz, 1H), 5.34 (ddq, *J* = 2.5, 2.0, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 15.1, 16.1, 16.9, 40.6, 41.9, 57.0, 64.0, 71.6, 74.4, 87.0, 106.5, 125.1, 143.8, 177.9, 180.2; HRMS (ESI), calcd for $C_{15}H_{18}O_5Na$ $(M+Na)^+$ 301.1052, found 301.1045.

Epoxide 42. A solution of **41** (27.5 mg, 98.8 μmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C and treated with dimethyldioxirane (0.08 M in acetone, 6.3 mL, 494 μmol). The resultant mixture was stirred at room temperature for 5 h. After concentration, the residue was purified with flash column chromatography (hexane/EtOAc 1:1 to 1:3) to give 24.6 mg of **42** (91%), along with 1.7 mg of diastereomer of **42** (5%): **42**: colorless crystal; m.p. 201-203 ºC; R_f = 0.21 (silica gel, 1:1 hexane/EtOAc); $[\alpha]^{28}_D$ –20.9 (*c* 0.37, CH_3OH); IR (film) 3403, 2948, 1768 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.11 (s, 3H), 1.17 (s, 3H), 1.55 (s, 3H), 2.08 (d, *J* = 16.5 Hz, 1H), 2.26 (dd, *J* = 16.5, 2.0 Hz, 1H), 2.59 (d, *J* = 19.0 Hz, 1H), 3.02 (d, *J* = 19.0 Hz, 1H), 3.95 (d, *J* = 9.0 Hz, 1H), 4.13 (s, 1H), 3.66 (d, *J* = 2.0 Hz, 1H), 4.48 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 16.1, 16.6, 17.9, 37.3, 38.5, 57.3, 64.8, 67.4, 69.4, 71.7, 75.8, 83.9, 108.3, 177.4, 180.2; HRMS (ESI), calcd for $C_{15}H_{18}O_6Na$ $(M+Na)^+$ 317.1001, found 317.0995.

(-)-Merrilactone A (1). A solution of epoxide **42** (10.4 mg, 35.3 μmol) in CH_2Cl_2 (3.5 mL) was treated with *p*-$TsOH\cdot H_2O$ (33.6 mg, 177 μmol), and the mixture was stirred at room temperature for 1 d.

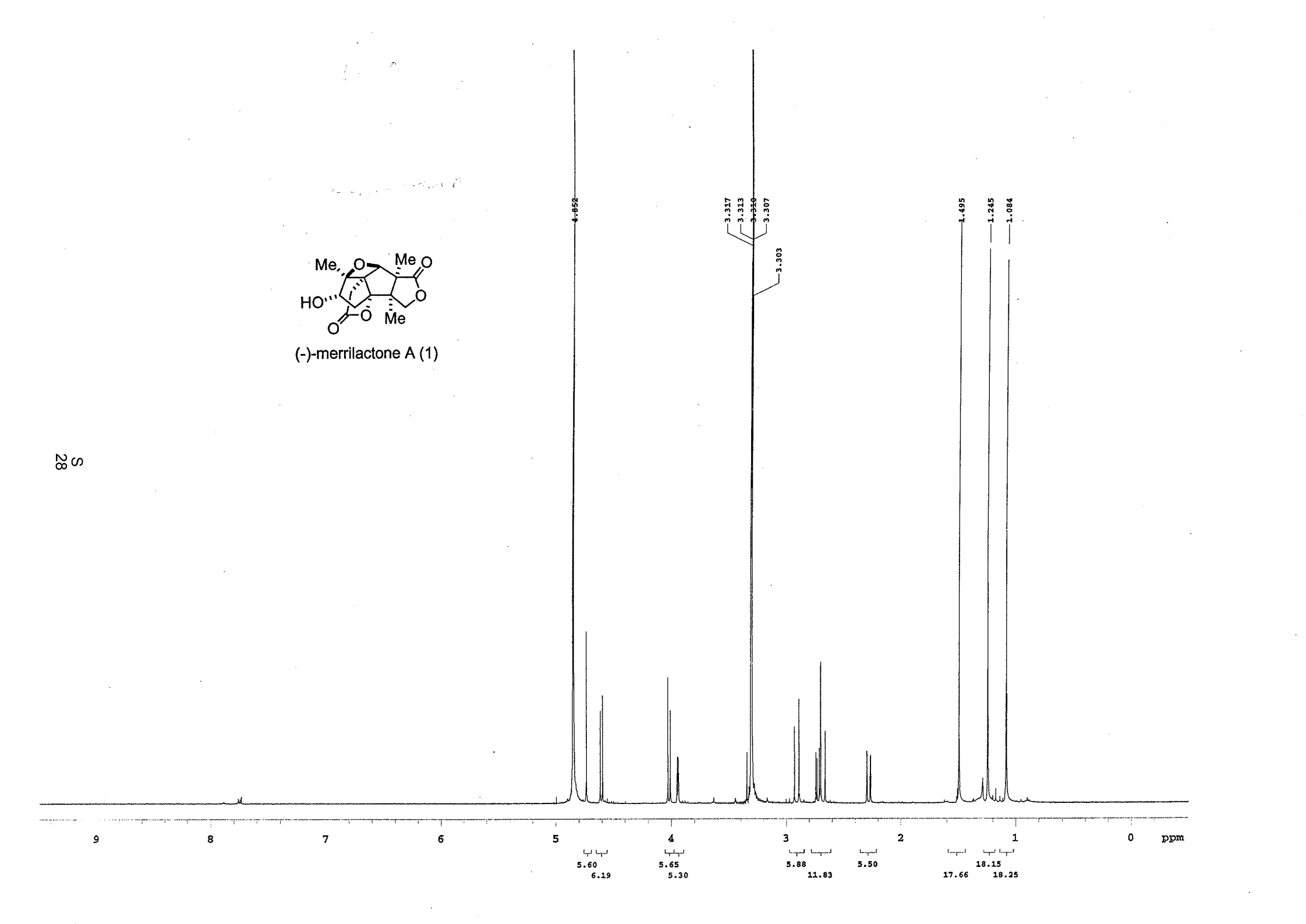
After filtration and concentration, the residue was purified with flash column chromatography (EtOAc) to give 10.0 mg of **1** (96%): colorless crystal; m.p. 263-266 ºC; R_f = 0.34 (silica gel, 1:3 hexane/EtOAc); $[\alpha]^{27}_D$ –15.7 (*c* 0.19, CH_3OH); IR (film) 3448, 2987, 1762 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.08 (s, 3H), 1.25 (s, 3H), 1.49 (s, 3H), 2.28 (dd, *J* = 15.5, 1.5 Hz, 1H), 2.68 (d, *J* = 19.5 Hz, 1H), 2.72 (dd, *J* = 15.5, 5.0 Hz, 1H), 2.91 (d, *J* = 19.5 Hz, 1H), 3.95 (dd, *J* = 5.0, 1.5 Hz, 1H), 4.02 (d, *J* = 10.0 Hz, 1H), 4.61 (d, *J* = 10.0 Hz, 1H), 4.74 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 16.0, 17.3, 17.5, 32.3, 44.1, 58.5, 61.2, 66.1, 75.5, 80.0, 90.4, 96.2, 107.3, 177.6, 179.3; HRMS (ESI), calcd for $C_{15}H_{18}O_6Na$ $(M+Na)^+$ 317.1001, found 317.0995.

To confirm absolute stereochemistry, synthetic merrilactone A (**1**) was converted to (+)- and (-)-MTPA esters, which were identical to the corresponding MTPA esters of natural merrilactone A (**1**).

(+)-MTPA-(-)-merrilactone A. (+)-MTPACl (3.8 μL, 20.4 μmol) was added to a solution of synthetic merrilactone A (**1**) (0.3 mg, 1.0 μmol) and DMAP (5.1 mg, 41.7 μmol) in CH_2Cl_2 (1.0 mL). The mixture was stirred for 3.5 h and filtrated through a pad of silica gel and concentrated. The residue was purified with HPLC (YMC-Pack R&D SIL-06, 150x4.6 mm, UV 254 nm, hexane/EtOAc 1:2, 1.0 mL/min, T_R = 5 min) to give 0.3 mg of (+)-MTPA-(-)-merrilactone A (59%): colorless oil; R_f = 0.23 (silica gel, 1:1 hexane/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.19 (s, 3H), 1.28 (s, 3H), 2.48 (d, *J* = 19.5 Hz, 1H), 2.52 (d, *J* = 17.0 Hz, 1H), 2.54 (d, *J* = 19.5 Hz, 1H), 3.01 (dd, *J* = 17.0, 5.0 Hz, 1H), 3.54 (s, 3H), 3.93 (d, *J* = 10.0 Hz, 1H), 4.56 (d, *J* = 10.0 Hz, 1H), 4.73 (s, 1H) 5.23 (d, *J* = 5.0 Hz, 1H), 7.45 (m, 5H); HRMS (ESI), calcd for $C_{25}H_{25}F_3O_8Na$ $(M+Na)^+$ 533.1394, found 533.1393.

(-)-MTPA-(-)-merrilactone A. (-)-MTPACl (7.5 μL, 40.0 μmol) was added to a solution of synthetic merrilactone A (**1**) (0.3 mg, 1.0 μmol) and DMAP (9.7 mg, 80.0 μmol) in CH_2Cl_2 (1.0 mL). The mixture was stirred for 2.0 h and filtrated through a pad of silica gel and concentrated. The residue was purified with HPLC (YMC-Pack R&D SIL-06, 150x4.6 mm, UV 254 nm, hexane/EtOAc 1:2, 1.0 mL/min, T_R = 8 min) to give 0.3 mg of (-)-MTPA-(-)-merrilactone A (59%): colorless oil; R_f = 0.23

(silica gel, 1:1 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.27 (s, 3H), 1.39 (s, 3H), 2.48 (d, *J* = 16.5 Hz, 1H), 2.55 (s, 2H), 3.02 (dd, *J* = 16.5, 5.0 Hz, 1H), 3.42 (s, 3H), 3.93 (d, *J* = 10.5 Hz, 1H), 4.55 (d, *J* = 10.5 Hz, 1H), 4.76 (s, 1H) 5.19 (d, *J* = 5.0 Hz, 1H), 7.43 (m, 5H); HRMS (ESI), calcd for $C_{25}H_{25}F_3O_8Na$ $(M+Na)^+$ 533.1394, found 533.1394.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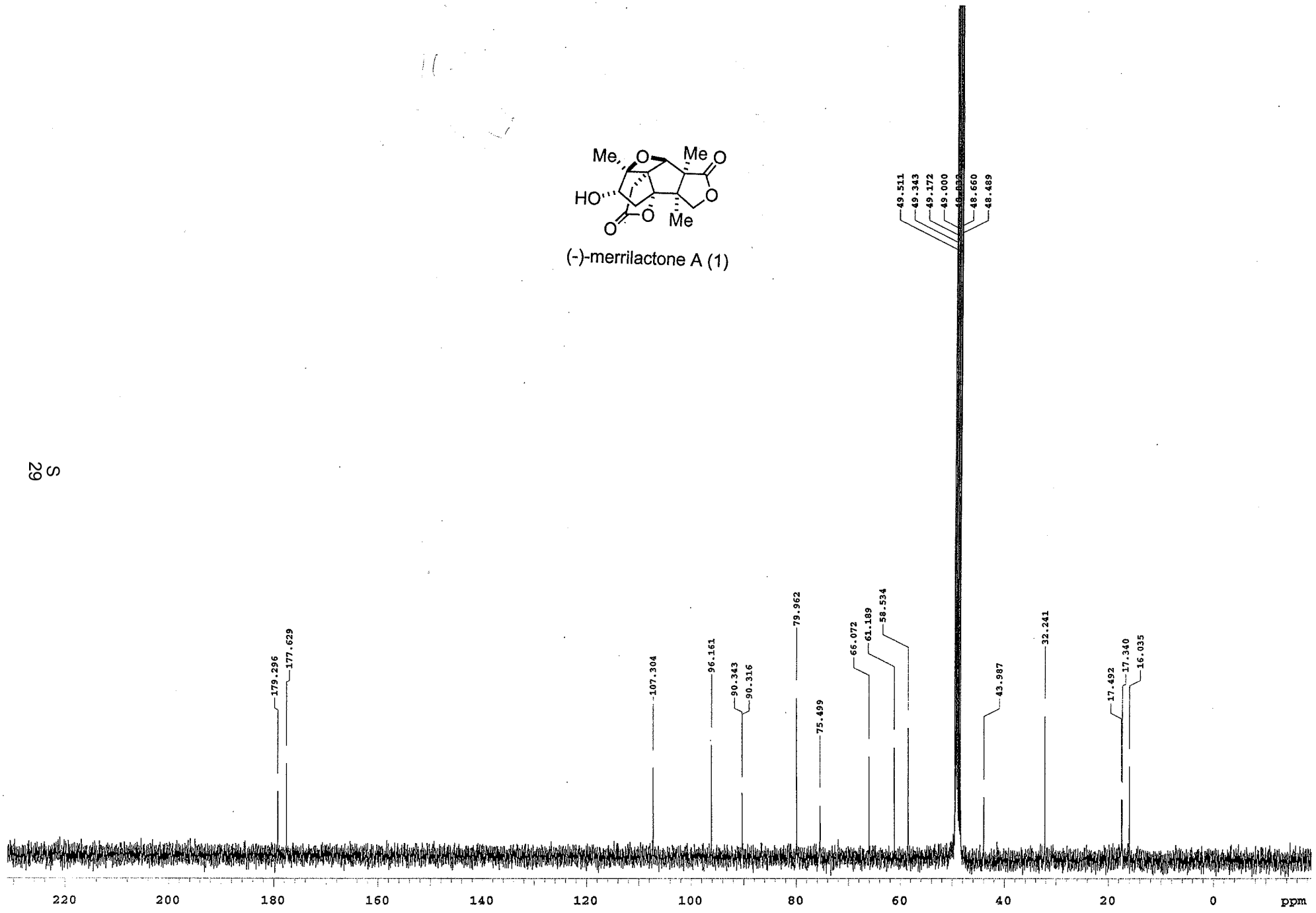
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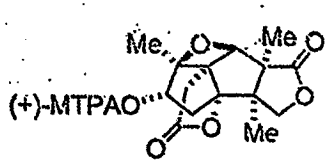

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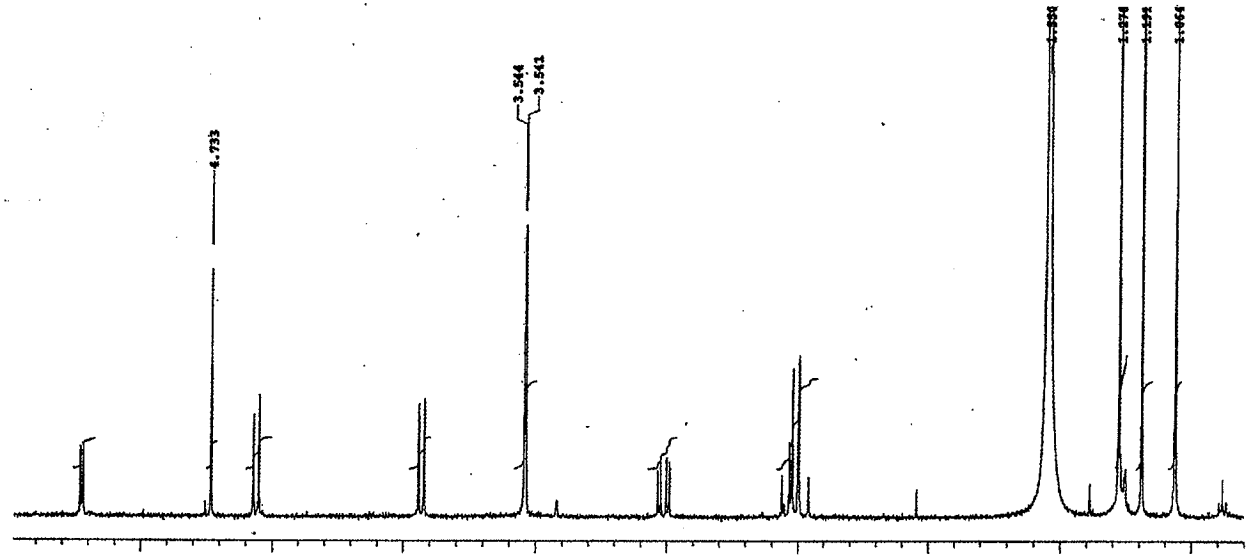
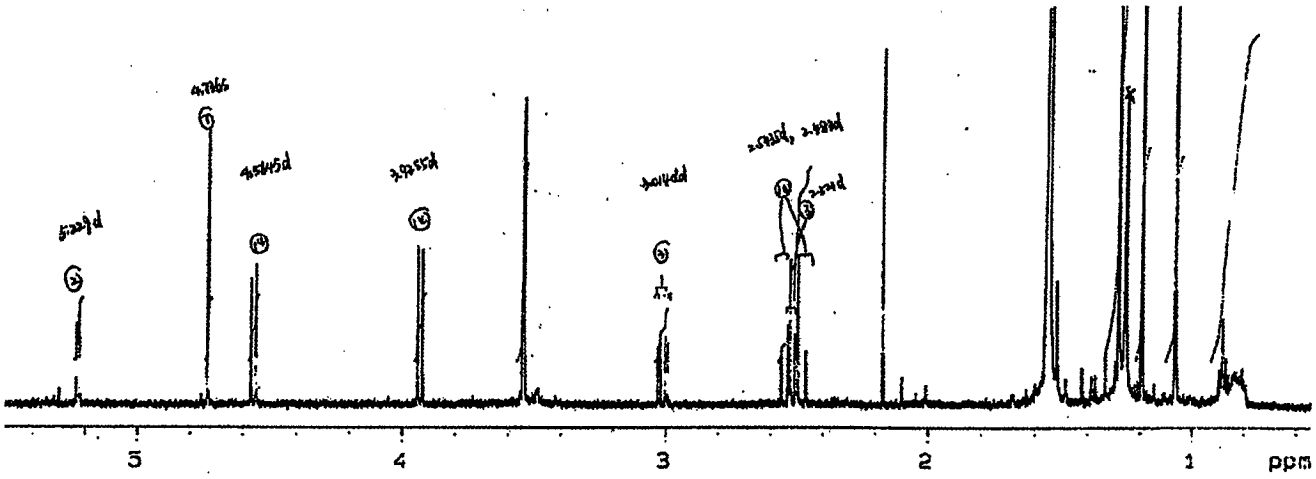
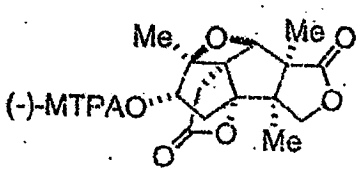


derived from natural product
($CDCl_3$, 600 MHz)





derived from synthetic sample
($CDCl_3$, 500 MHz)

derived from natural product
($CDCl_3$, 600 MHz)