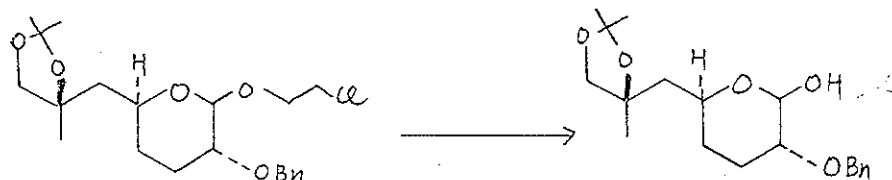


To a solution of the diol ___ (0.90 g, 2.49 mmol) in a mixture of 2,2-dimethoxypropane (2 mL) and CH_2Cl_2 (10 mL) was added PPTS (5 mg). After stirring at room temperature for 5 hr, the reaction mixture was poured into aq NaHCO_3 . The separated organic layer was dried (Na_2SO_4), and concentrated under reduced pressure to afford the acetonide ___ (0.90 g, yield 91%).

15029



To a solution of the chloroethyl glycoside ___ (248 mg, 0.62 mmol) dissolved in DMF (8 mL) was added benzenesulfinic acid sodium salt (0.60 g, 3 mmol) and potassium iodide (1.0 g, 6 mmol). The reaction mixture was heated under nitrogen atmosphere at 100°C for 10 hr, and then poured into H₂O. The aqueous layer was extracted with ether (x3), and the combined organic layer was washed (H₂O, sat. NaCl), dried (Na₂SO₄), and concentrated under reduced pressure. Tlc purification of the resulting residue gave the lactol ___ (150 mg, yield 72 %).



To a solution of the lactol --- (150 mg, 0.45 mmol) in a mixture of acetic acid buffer (3 mL) and DMF (2 mL) cooled to 0°C was added bromine (100 μ L, 3.9 mmol) dropwise. After stirring at 0°C for 30 min, aq. NaHSO_3 was added to decompose excess bromine. The aqueous layer was extracted with ether (x3), and the extracts were washed (H_2O , sat. NaHCO_3 , sat. NaCl), and dried (Na_2SO_4). Purification of the residue on preparative tlc gave the lactone --- (81 mg, yield 54%).

2位の不斉中心に因りて混合物。(9:1)

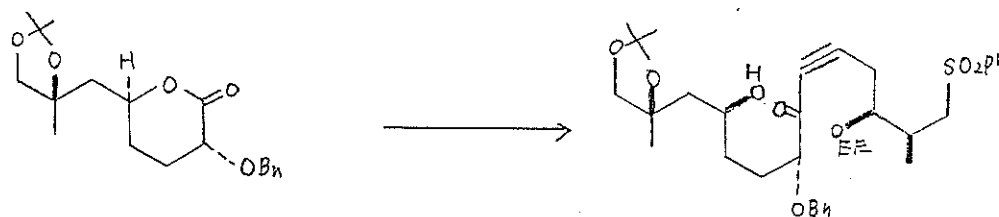
$$[\alpha]_D^{25} = +87.3^\circ \quad (C = 1.04, \text{CHCl}_3)$$

$$\text{IR} \quad 1745 \text{ cm}^{-1}$$

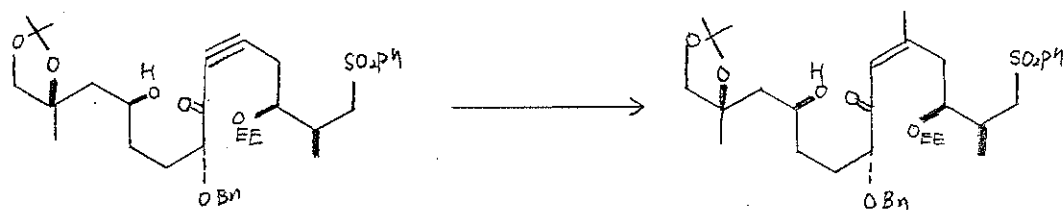
$^1\text{H NMR}$; δ 1.35 (6H, $\Delta \times 2$), 1.39 (3H, Δ), 1.6–2.2 (6H), 3.76–3.88 (2H, AB), 3.95 (1H, m), 4.63–4.92 (2H, AB), 4.72 (1H, m), 7.3–7.4 (5H).

Analysis; Found C, 68.21; H, 7.78.

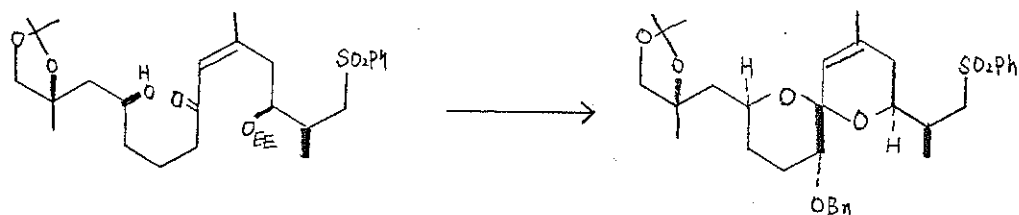
Calcd for $\text{C}_{19}\text{H}_{26}\text{O}_5$: C, 68.24; H, 7.84.



To a solution of the acetylene ___ (117 mg, 0.35 mmol) dissolved in THF (4 mL) cooled to -78°C under nitrogen atmosphere was added n-BuLi (1.55 M, 0.35 mL, 0.54 mmol) dropwise. After stirring at -78°C for 15 min, lactone ___ (117 mg, 0.35 mmol) in THF (1 mL) was introduced and the stirring was continued for 15 min. The solution was poured into aq. NH_4Cl , and the separated aqueous layer was extracted with ether. The combined extracts were washed (H_2O x2, sat. NaCl), dried (Na_2SO_4), and concentrated under reduced pressure to afford the crude oil. Purification of this oil on preparative tlc gave the acetylene ketone ___ (185 mg, yield 80%).

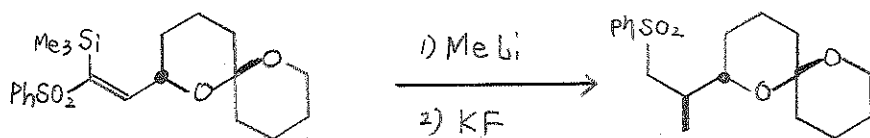


To a stirred slurry of CuI (128 mg, 0.67 mmol) in ether (3 mL) cooled to 0°C under nitrogen atmosphere was added MeLi (1.5 M solution in ether, 0.80 mL, 1.2 mmol) dropwise. After stirring at 0°C for 20 min, the solution was cooled to -78°C and the acetylene ketone 2 (91 mg, 0.14 mmol) in ether (1 mL) was added. After stirring at -78°C for 15 min, the reaction mixture was quenched by the addition of sat. NH₄Cl solution. The aqueous layer was extracted with ether (x3) and the extracts were washed (H₂O, sat NaCl), dried (Na₂SO₄) and concentrated under reduced pressure to give the Z-olefin 4 (80 mg, yield 87%).



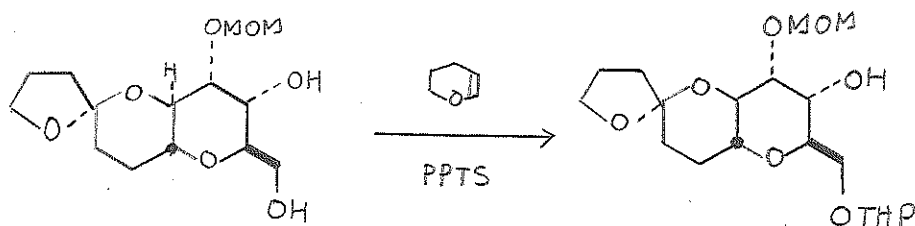
A solution of the enone --- (141 mg, 0.21 mmol) and PPTS (10 mg) dissolved in MeOH (3 mL) was stirred at room temperature for 2.5 hr. The reaction mixture was poured into sat. NaHCO_3 , and the aqueous layer was extracted with ether (x3). The extracts were washed (H_2O , sat. NaCl), dried (Na_2SO_4), and concentrated under reduced pressure to afford the oil.

A solution of this oil dissolved in a mixture of CH_2Cl_2 and 2,2-dimethoxypropane (0.3 mL) in the presence of PPTS (10^2 mg) was stirred at room temperature overnight. The reaction mixture was poured into sat. NaHCO_3 , and the aqueous layer was extracted with ether (x3). The combined organic layers were washed (H_2O , sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified on preparative silica gel tlc to afford the segment A --- (36 mg, yield 29 %).



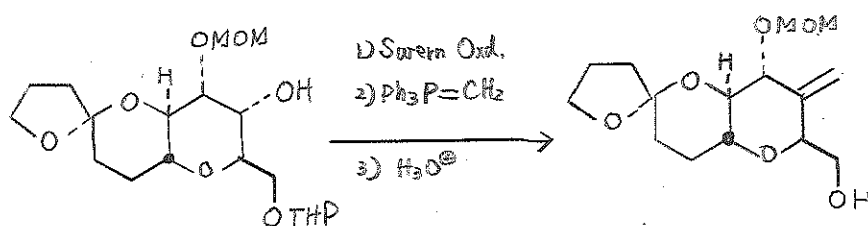
To a solution of the spiro heterocycle ~ (482 mg, 1.3 mmol) dissolved in THF (15 ml) cooled to -78°C under nitrogen atmosphere was added methyllithium (1.5 M solution in ether, 2.6 ml, 3.9 mmol) dropwise. The reaction mixture was stirred at -78°C for 30 min and then warmed up to -10°C over 30 min. Addition of saturated aqueous ammonium chloride was followed by three portions of ether. The combined organic layer was washed (H_2O , NaCl), dried (Na_2SO_4) and then concentrated under reduced pressure to afford the adduct (482 mg, yield 96%) as an oil.

This oil was dissolved in methanol (15 ml) and then treated with potassium fluoride (0.15 g) overnight. The solvent was removed in vacuum, and the resulting residue was taken up in ether. The ether solution was washed (H_2O , NaCl), dried (Na_2SO_4) and then concentrated under reduced pressure to provide ~ (378 mg, yield 85%).

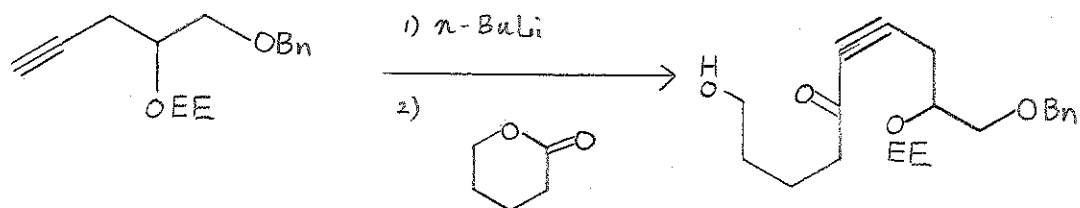


A solution of the diol ~ (127mg, 0.42mmol) and dihydropyran (0.30ml, 3.2mmol) dissolved in dichloromethane (9ml) in the presence of pyridinium p-toluenesulfonate (PPTS, 10mg) was stirred at -20°C for two days. The reaction mixture was poured into aq. sodium bicarbonate and the separated aqueous layer was extracted with dichloromethane. a portion of

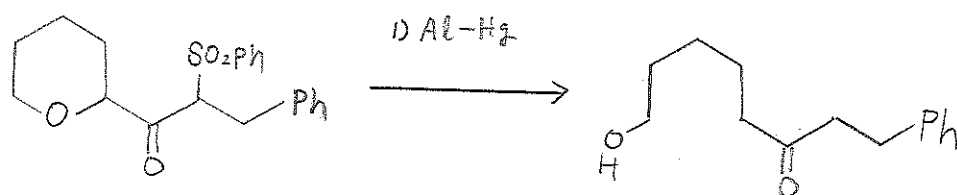
The combined organic layer was dried (Na_2SO_4) and then concentrated under reduced pressure to afford the oil (0.21g). Purification of this oil by silica-gel (4g) chromatography with ether as eluant provided the tetrahydropyranyl ether ~ (81mg, yield 50%) as diastereoisomers.



- 1) Swern oxidation of the alcohol (81 mg, 0.21 mmol) under the usual conditions (oxalyl chloride 0.10 ml, DMSO 0.20 ml, triethylamine 0.60 ml) described before provided the corresponding ketone (61 mg) in yield of 75%.
- 2) To a solution of methyltriphenylphosphonium bromide (294 mg, 0.82 mmol) in tetrahydrofuran (4.5 ml) cooled to 0°C was added *n*-butyllithium [1.65 M solution in hexane, 0.50 ml, 0.83 mmol] dropwise. The solution was stirred at room temperature for 30 min, and then cooled to -78°C. A solution of the ketone (61 mg) in tetrahydrofuran (0.5 ml) was introduced to this solution of methylenetriphenylphosphorane, and the cooling bath was removed. This reaction mixture was heated under reflux overnight, and usual etherial work up gave the crude oil (132 mg), which is purified by silica gel chromatography with ether/hexane 1:1 as eluant to provide the exomethylene product (36 mg, yield 59%).
- 3) This product (36 mg, 0.094 mmol) was dissolved in methanol (1.5 ml) and then heated at 50°C for 3 hr in the presence of PPTS (4 mg). The solution was poured into aq. sodium bicarbonate solution, and then extracted with three portions of ether. The combined organic layer was washed with water and saturated aq. NaCl, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting oil was purified by silica gel (0.68) chromatography with ether/hexane 3:1 as eluant to afford ~ (27 mg, yield 96%).



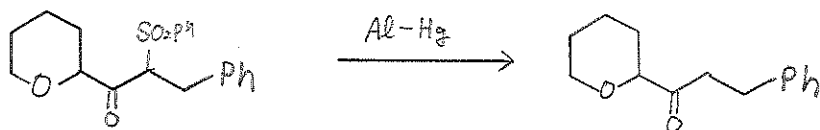
To a solution of acetylene \sim (1.44g, 5.5 mmol) dissolved in tetrahydrofuran (55 ml) cooled to -78°C under nitrogen atmosphere was added n -butyllithium (1.55 M solution in hexane, 4.4 ml, 6.82 mmol) dropwise. After stirring for 15 min, δ -valerolactone (1.1g, 10.1 mmol) in tetrahydrofuran (3 ml) was introduced. The stirring was continued for 30 min at -78°C , and then the reaction was quenched by the addition of saturated aq. NH_4Cl solution. The separated aqueous layer was extracted with three portions of ether, and the combined organic layer was washed (H_2O , NaCl), dried (Na_2SO_4) and then concentrated under reduced pressure. The resulting oil (2.60g) was purified by silica gel (30g) chromatography with ether/hexane 3:1 as eluant to provide the ynone \sim (1.6g) in yield of 80%.



Aluminum amalgam was prepared from aluminum foil (0.20g) according to the procedures described before. This aluminum amalgam was added to a solution of the keto-sulfone ~ (115mg, 0.32mmol) in *n*-propanol (4.5 ml) and water (0.45 ml). a mixture of

The reaction mixture was stirred at room temperature for 2 hr, and usual work up (ether extraction) gave the alcohol ~ (54mg, yield 78%).

The resulting product ~ was acetylated under usual conditions (acetic anhydride 0.5ml, pyridine 1ml, stirring at room temperature overnight) to afford the corresponding acetate.



To a solution of the keto-sulfone ~ (60 mg, 0.17 mmol) dissolved in a mixture of tetrahydrofuran (3 ml) and water (0.30 ml) was added aluminum amalgam (prepared from 50 mg of aluminum foil). The stirring was continued at room temperature for 1.2 hr, and usual work up (ether extraction) gave the corresponding ketone ~ (35 mg, yield 94%).



To a suspension of sodium hydride (1.4 g, 34 mmol, washed with hexane before use) dissolved in a mixture of benzyl bromide (3.0 mL, 26 mmol), THF (20 mL) and DMF (10 mL) cooled to 0°C was added glycidol (2 mL, 31.5 mmol) dropwise. After stirring at 0°C for 30 min, the cooling bath was removed, and then stirring was continued for 6 hr. The reaction mixture was poured into water, and the aqueous layer was extracted with ether (x3). The combined organic layers were washed (H₂O, sat. NaCl), dried (Na₂SO₄) and concentrated under reduced pressure. Distillation of the resulting oil at 140°C in vacuum (20 mmHg) provided the benzyl ether --- (3.18 g, yield 75%).

¹H nmr δ 2.4-2.5 (2H), 3.10 (1H, m), 3.2-3.7 (2H), 4.44 (2H, s), 7.1-7.2 (5H).



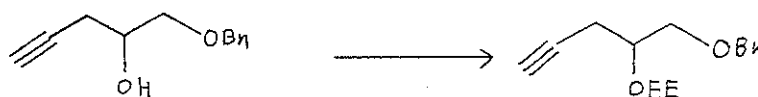
1) To a solution of (trimethylsilyl)acetylene (3.3 mL, 31.7 mmol) in THF (80 mL) cooled to -78°C under nitrogen atmosphere was added n-BuLi (1.55M solution in hexane, 22.5 mL, 34.9 mmol) dropwise. After stirring for 20 min, $\text{BF}_3 \cdot \text{OEt}_2$ (2.9 mL, 23.6 mmol) was added and the stirring was continued for 15 min. To this solution was added the epoxide 5-69 (3.18 g, 19.4 mmol) in THF (5 mL) dropwise. After stirring at -78°C for 1 hr, the reaction mixture was poured into sat. NaHCO_3 solution and the aqueous layer was extracted with ether (x3). The extracts were washed (H_2O , sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to give the alcohol 5-70 (5.5 g).

2) A solution of the oil and potassium fluoride (4.5 g) dissolved in MeOH (80 mL) was heated at reflux temperature for 1 hr. The solvent was removed by evaporation, and the resulting oil was dissolved in ether. The ethereal solution was washed (H_2O , sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude product (3.6 g). Distillation at 120°C in vacuum (5 mm Hg) provided the acetylene --- (3.04 g, yield 82 %).

^1H nmr δ 2.01(1H, t, $J=3$), 2.40-2.47(2H), 3.63(1H), 3.45-3.63(2H, AB), 3.96(1H, br), 4.55(2H, s), 7.2-7.4(5H).

IR (CHCl_3) 3600, 3320, 2130cm^{-1} .

Found C 75.72, H 7.44; Calcd C 75.76, H 7.42, for $\text{C}_{12}\text{H}_{14}\text{O}_2$.



To a solution of the acetylene ___ (3.04 g, 16 mmol) and PPTS (0.20 g) dissolved in CH_2Cl_2 (20 mL) was added ethyl vinyl ether (5 mL) dropwise. After stirring at room temperature for 3.5 hr, the reaction mixture was poured into sat. NaHCO_3 . The separated organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford the ethoxy ethyl ether ___ (3.97 g, yield 95%) as an oil. Purification of this oil on silica gel chromatography (60 g) with 1:15 ether/hexane as eluant provided the compound (2.8g, yield 67 %) which was pure enough to use in the next step.



To a stirred slurry of CuI (0.62 g, 3.2 mmol) in ether (6 mL) cooled to 0°C under nitrogen atmosphere was added MeLi (1.5 M solution in ether, 4.3 mL, 6.5 mmol) dropwise. After stirring at 0°C for 20 min, the solution was cooled to -78°C and the acetylene ketone 5-74 (150 mg, 0.41 mmol) in ether (1 mL) was added. After stirring at -78°C for 15 min, the reaction mixture was quenched by the addition of sat. NH₄Cl solution. The aqueous layer was extracted with ether (x3) and the extracts were washed (H₂O, sat NaCl), dried (Na₂SO₄) and concentrated under reduced pressure to give the Z-olefin 2 4 (147 mg, yield 95%).

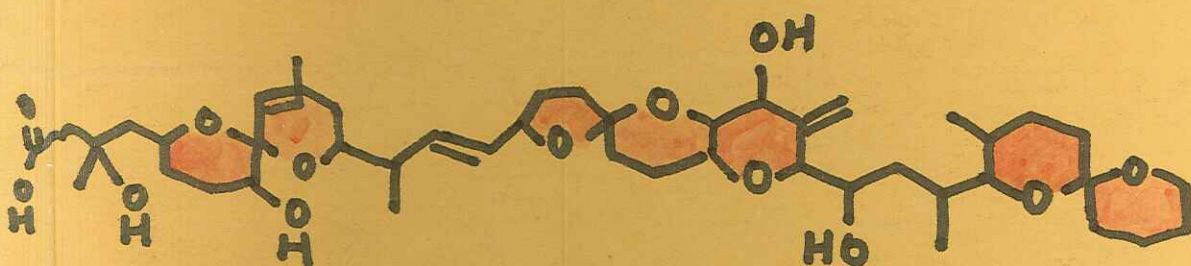
IR (CHCl₃) 3500, 2220, 1670cm⁻¹.



A solution of the enone ___ (147 mg, 0.39 mmol) and PPTS (10 mg) dissolved in MeOH (3 mL) was stirred at room temperature overnight. The reaction mixture was poured into sat. NaHCO_3 , and the aqueous layer was extracted with ether (x3). The combined organic layers were washed (H_2O , sat. NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting ²oil⁴ was purified on preparative silica gel tlc to afford the spiro-compound ___ (85 mg, yield 72 %).

¹H nmr δ 1.4-2.1(8H), 1.71(3H, s), 3.5-3.7(3H), 3.90(1H, td, J=12, 3), 4.16(1H, m), 4.64(2H, s), 5.35(1H, d, J=1), 7.2-7.4(5H).

Found C 75.11, H 8.44; Calcd C 74.97, H 8.39, for $\text{C}_{18}\text{H}_{24}\text{O}_3$..pa



Y. ~~Chikawa~~

Cセグメント. Bセグメント. B+C.

SYNTHETIC STUDY OF OKADAIC ACID

