# Synthesis of 2-Methylsulfonylmethyl-3,4,5-trimethoxybenzyl Methyl Ether. Confirmation of the Structure of Two Pyrogallols Isolated from Red Alga

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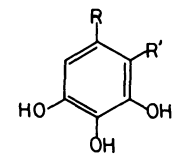
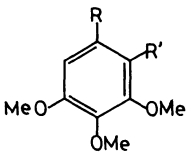
**Synopsis.** 2-Methylsulfonylmethyl-3,4,5-trimethoxybenzyl methyl ether was synthesized in 4 steps from methyl 3,4,5-trimethoxybenzoate, confirming the structure of the natural phenol.

We recently reported the isolation of 3,4,5-trihydroxybenzyl methyl ether (**1**) and 2-methylsulfonylmethyl-3,4,5-trihydroxybenzyl methyl ether (**2**) from the red alga *Grateloupia filicina* (Wulfen) J. Agardh.[1] Both of the compounds showed moderate antibacterial activity against *Bacillus substilis*. Described here is our attempted approach to the unique sulfone (**2**), resulting in the synthesis of its trimethyl derivative (**11**). The complete identity of synthetic **11** and the derivative from the natural product denied the possibility of another structure (**3**) for the sulfone.

3,4,5-Trimethoxybenzyl alcohol was treated with sodium hydride and methyl iodide to give a methyl ether (**4**), whose spectral and physical properties were identical with those of the derivative from the natural phenol (**1**). Compound **4** was exposed to chloromethyl methyl sulfide and tin(IV) chloride,[2] giving not the desired sulfide (**9**) but the chloride (**5**) as a major product. Under the same conditions, however, methyl 3,4,5-trimethoxybenzoate (**6**) could be converted smoothly to sulfide (**7**) in 70% yield. **7** was reduced with lithium aluminum hydride to alcohol (**8**). In contrast to the preparation of **4**, treatment of **8** with methyl iodide and sodium hydride produced many compounds containing low yield of the desired methyl ether (**9**). When **8** was heated in refluxing methanol in the presence of *p*-toluenesulfonic acid,[3] **9** was obtained in 53% yield,[4] accompanied by the pentamethoxy compound (**10**). Oxidation of the sulfide (**9**) proceeded cleanly with excess *m*-chloroperbenzoic acid, affording the sulfone (**11**).




(1) R=$CH_2OMe$, R'=H
(2) R=$CH_2OMe$, R'=$CH_2SO_2Me$
(3) R=$CH_2SO_2Me$, R'=$CH_2OMe$




(4) R=$CH_2OMe$, R'=H
(5) R=$CH_2Cl$, R'=H
(6) R=$CO_2Me$, R'=H
(7) R=$CO_2Me$, R'=$CH_2SMe$
(8) R=$CH_2OH$, R'=$CH_2SMe$
(9) R=$CH_2OMe$, R'=$CH_2SMe$
(10) R=$CH_2OMe$, R'=$CH_2OMe$
(11) R=$CH_2OMe$, R'=$CH_2SO_2Me$
(12) R=$CH_2SMe$, R'=$CH_2OMe$

Fig 1.

The last stage toward **2** in our plan was the cleavage of all of the methyl ether on **11** and selective methylation of the benzylic hydroxyl group. Unfortunately, all trials for demethylation of **11** were unsuccessful despite use of various conditions using boron tribromide,[5] aluminum chloride–ethanethiol[6] and sodium iodide–chlorotrimethylsilane.[7]

To confirm the structure of **2**, then, natural phenol was converted to **11** with methyl iodide and sodium hydride. The spectral and physical properties of synthetic **11** and the derivative from the natural product were identical in all respects.

## Experimental

**3,4,5-Trimethoxybenzyl Methyl Ether (4).** To a solution of 3,4,5-trimethoxybenzyl alcohol (973 mg, 4.91 mmol) in dry THF (80 ml), was added sodium hydride (60% suspension, 245 mg, 6.13 mmol) and methyl iodide (3.49 ml, 56.1 mmol) at room temperature. After stirring for 12 h, aqueous ammonium chloride was added to the mixture and THF was evaporated. The aqueous residue was extracted with ether and the organic layer was dried ($Na_2SO_4$) and evaporated. Column chromatography on silica gel using ethyl acetate–hexane (1:1) gave **4** (885 mg, 93%) as an oil. IR ($CHCl_3$) $\nu$ 1593, 1503, 1035 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=3.41 (3H, s, $CH_2O\underline{CH_3}$), 3.85 (3H, s, $OCH_3$, 4 position), 3.87 (6H, s, $OCH_3$, 3 and 5 position), 4.40 (2H, s, $\underline{CH_2}OCH_3$), 6.60 (2H, s, aromatic). Found: *m/z* 212.1048. Calcd for $C_{11}H_{16}O_4$: M, 212.1048.

**Methylation of the Natural Phenol (1).** To a solution of the phenol (**1**) (18.3 mg, 0.107 mmol) in THF (2 ml), was added sodium hydride (60% suspension, 40 mg, 1.0 mmol), methyl iodide (0.5 ml, 8 mmol), and dimethyl sulfoxide (1 ml) as a cosolvent. After refluxing overnight, water and ethyl acetate was added to the mixture. The organic layer was dried ($MgSO_4$) and evaporated to give the crude product. Purification by preparative TLC using ethyl acetate–benzene (1:2) gave **4** (15.0 mg, 66%) as an oil. The IR, $^1H$ NMR, mass spectrum and the $R_f$ value of TLC in various solvent system were identical with those of the synthetic sample.

**Methyl 2-Methylthiomethyl-3,4,5-trimethoxybenzoate (7).** To a solution of methyl 3,4,5-trimethoxybenzoate (**6**) (1.152 g, 5.10 mmol) and chloromethyl methyl sulfide (0.55 ml, 6.6 mmol) in dry dichloromethane (15 ml), was added tin(IV) chloride (0.19 ml, 1.6 mmol) at 0°C. Another portions of tin(IV) chloride (0.19 ml and 0.10 ml, 2.5 mmol totally) was added to the mixture, while the reaction was carried out at room temperature for 7 h. After addition of aqueous sodium hydrogencarbonate, the organic layer was dried ($Na_2SO_4$) and evaporated. The crude product was purified by column chro-

matography on silica gel using ethyl acetate–hexane (1:3—1:1) as eluent to give **7** (1.098 g, 70%) as an oil. IR ($CHCl_3$) $\nu$ 1717 $cm^{-1}$ (ester CO); $^1H$ NMR ($CDCl_3$), $\delta$=2.03 (3H, s, $SCH_3$), 3.85 (3H, s, $OCH_3$), 3.88 (9H, s, $OCH_3$), 4.09 (2H, s, $SCH_2$–), 7.20 (1H, s, aromatic); MS *m/z* (rel intensity) 286 (26, $M^+$), 255 (6), 239 (100), 224 (15), 179 (7). Found: *m/z* 286.0888 Calcd for $C_{13}H_{18}O_5$: M, 286.0876.

**2-Methylthiomethyl-3,4,5-trimethoxybenzyl Alcohol (8).** To a suspension of lithium aluminum hydride (233 mg, 6.14 mmol) in dry ehter (30 ml), was added a solution of **7** (1.057 g, 3.70 mmol) in ehter (5 ml) at 0°C. After stirring at room temperature for 2 h and destroying the excess hydride with ethyl acetate, 10% aqueous sodium hydroxide was added until white aluminum oxide separates. The organic layer was dried ($Na_2SO_4$) and evaporated. Purification by column chromatography on silica gel using ethyl acetate–hexane (1:1) as eluent gave **8** (835 mg, 87%) as an oil. IR ($CHCl_3$) $\nu$ 3426 $cm^{-1}$ (alcohol); $^1H$ NMR ($CDCl_3$) $\delta$=2.07 (3H, s, $SCH_3$), 3.78—3.88 (9H, $OCH_3$), 4.63 (2H, bd, $J$=3.5 Hz, $CH_2OH$), 6.74 (1H, s, aromatic); MS *m/z* (rel intensity) 258 (3, $M^+$), 211 (100), 196 (22), 181 (14), 152 (16), 61 (7). Found: *m/z* 258.0976 ($M^+$). Calcd for $C_{12}H_{18}O_4S$: M, 258.0926.

**2-Methylthiomethyl-3,4,5-trimethoxybenzyl Methyl Ether (9).** A solution of **8** (90.2 mg, 0.35 mmol) and *p*-toluenesulfonic acid (7 mg, 0.04 mmol) in methanol (5 ml) was refluxed for 6 h. After addition of aqueous sodium hydrogencarbonate, methanol was evaporated and the aqueous residue was extracted with ether. The organic layer was dried ($Na_2SO_4$) and evaporated. The crude product was chromatographed on silica gel using ethyl acetate–hexane (1:3) as eluent to give **9** (50.1 mg, 53%) as an oil. IR ($CHCl_3$) $\nu$ 1124 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=2.05 (3H, s, $SCH_3$), 3.38 (3H, s, $CH_2O\underline{CH_3}$), 3.74—3.87 (11H, $\underline{CH_2}S$ and three $OCH_3$), 4.48 (2H, s, $\underline{CH_2}OCH_3$), 6.64 (1H, s, aromatic); MS *m/z* (rel intensity) 272 (1, $M^+$), 224 (100), 209 (20), 195 (99), 180 (14). Found: *m/z* 272.1079. Calcd for $C_{13}H_{20}O_4S$: M, 272.1081.

**2-Methylsulfonylmethyl-3,4,5-trimethoxybenzyl Methyl Ether (11).** To a solution of **9** (282 mg, 1.04 mmol) in dry dichloromethane (10 ml), was added sodium hydrogencarbonate (342 mg, 4.07 mmol) and then *m*-chloroperbenzoic acid (710 mg, 4.10 mmol) at room temperature. After stirring for 2 h, aqueous sodium sulfite, aqueous sodium hydrogencarbonate and dichloromethan was added to the mixture. The organic layer was dried ($Na_2SO_4$) and evaporated. Purification by column chromatography on silica gel using ethyl acetate–hexane (1:1) as eluent gave **11** (207 mg, 66%) as solid, which was recrystallized from ether. Mp 94.5—96.5°C; IR ($CHCl_3$) $\nu$ 1600, 1499, 1461, 1412, 1310, 1197, 1127 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=2.80 (3H, s, $SO_2CH_3$), 3.40 (3H, s, $CH_2O\underline{CH_3}$), 3.83, 3.87, 3.93 (each 3H, s, $OCH_3$), 4.44, 4.57 (each 2H, s, $CH_2S$ and $CH_2O$) 6.77 (1H, s, aromatic); MS *m/z* (rel intensity) 304 (2, $M^+$), 225 (48), 195 (100), 180 (13). Found: *m/z* 304.1017. Calcd for $C_{13}H_{20}O_6S$: M, 304.0980.

**Methylation of 2-Methylsulfonylmethyl-3,4,5-trihydroxybenzyl Methyl Ether (2).** A solution of **2** (2.5 mg, 0.0095 mmol) in THF (0.5 ml) was treated with sodium hydride (60% suspension in mineral oil, 2 mg, 0.05 mmol) and methyl iodide (0.2 ml, 5 mmol) for 24 h at room temperature, and refluxed overnight. Aqueous ammonium chloride was added to the mixture, which was extracted with dichloromethane and the organic layer was dried ($Na_2SO_4$) and evaporated. Preparative TLC on silica gel using ethyl acetate–hexane (1:1) as solvent gave **11** (0.7 mg, 24%). The IR, $^1H$ NMR, mass spectra, the GC retention time, and the $R_f$ value of TLC in various solvent system were identical with those of the synthetic sample.

## References

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2) I. Fleming and J. Iqbal, *Synthesis*, **1982**, 937.

3) The facility of the benzyl cation formation in the reaction **4**→**5** stimulated us to use these conditions.

4) We carried out the NOE experiment for the compound, because formation of the isomer (**12**) is also possible by neighbouring participation of the sulfur atom. The NOEs obtained by each irradiations of the related protons (aromatic and $\underline{CH_2}OCH_3$) were predictable only from the structure (**9**). We thank Dr. Kazunobu Noumi, Pharmaceuticals Research Center, Kanebo, Ltd. for the experiment.

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