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Synthesis of a Cyclic 3-Methylsulfonyl Enol Ether

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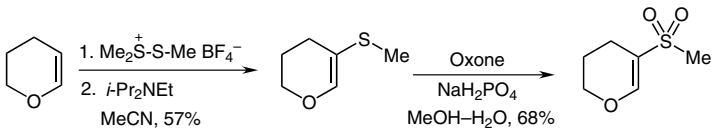
Dedicated to Professor Hans-Ulrich Reissig on the occasion of his 66th birthday



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Abstract Electrophilic introduction of a methylmercapto group into dihydropyran gives 3-methylmercaptodihydropyran, which is readily oxidized to 3-methylsulfonyldihydropyran.

Key words enol ether, methylmercapto, methylsulfonyl, methylsulfinyl, oxidation, Oxone

During the studies on new chemically stable analogues of the very labile natural prostacyclin **1a** we synthesized the chemically stable and biologically potent 5-cyanoprostacyclin **1b** (nileprost),[2] and wondered whether analogous chemically stable prostacyclin analogues with an electron-attracting 5-methylsulfoxide group **1c** or in particular with a 5-methylsulfone group **1d** might also be chemically stable and biologically active (Figure 1).

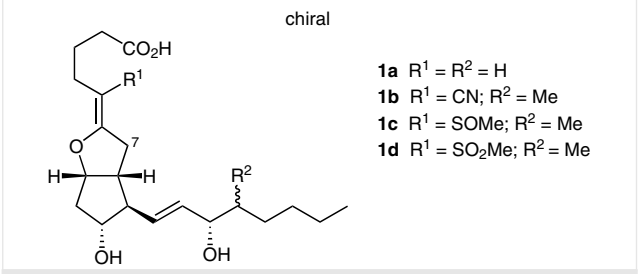
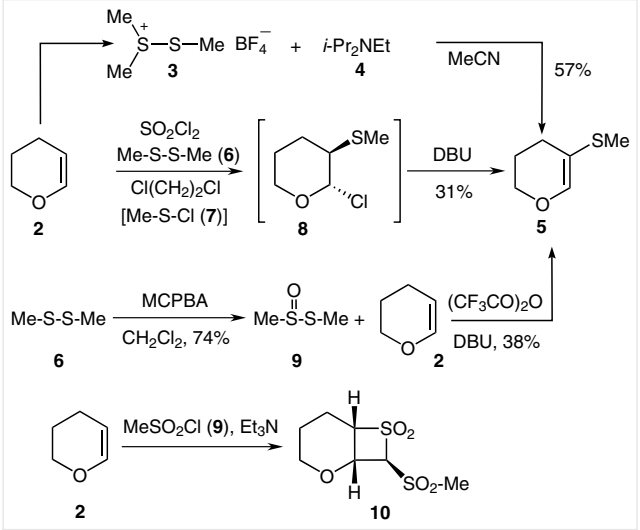


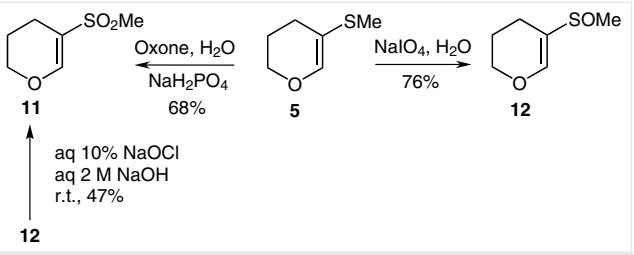
Figure 1 Prostacyclin analogues

We thus studied the reaction of dihydropyran (**2**) as a model for the enol ether moiety in prostacyclin **1a** with dimethylmethylmercaptosulfonium tetrafluoroborate (**3**)[3] in the presence of diisopropyl ethylamine (**4**, Hünig's base) in acetonitrile, whereupon 57% of the redistilled known 3-methylmercaptodihydropyran (**5**)[4] was obtained (Scheme 1). Alternatively, reaction of **2** with methylsulfenyl chloride (**7**), prepared in situ from dimethyl disulfide (**6**) with SO_2Cl_2,[5] gave the crude chloride **8**,[4] which was not isolated and characterized, but dehydrohalogenated in situ with DBU followed by distillation to give 3-methylmercaptodihydropyran (**5**) in 37% yield. Oxidation of dimethyl disulfide (**6**) with *m*-chloroperbenzoic[6] acid afforded the sulfoxide **9**, which underwent a Pummerer type reaction[7] with trifluoroacetic acid anhydride in the presence of **2** to provide the unsaturated sulfide **5** in 38% yield. Yet, the reaction of dihydropyran **(2)** with $MeSO_2Cl$ (**9**)/Et_3N to introduce the methylsulfonyl group in one reaction step did not give any of the desired sulfone **11** but instead the known crystalline bicyclic adduct **10**[8–10] (Scheme 1).



Scheme 1

Oxidation of **5** with Oxone in water afforded the crystalline and chemically stable sulfone **11** in 68% yield, whereas reaction of **5** with aqueous $NaIO_4$ furnished 76% of the racemic sulfoxide **12**, which is readily oxidized in 47% yield by NaOCl in H_2O–acetonitrile to the desired sulfone **11** (Scheme 2). The described exploring experiments are not as yet optimized.



Scheme 2

The high biological potency of our prostacyclin(carbacyclin) analogues iloprost[11] and the even more potent cicaprost[12] caused us then to abandon the synthesis of further new prostacyclin analogues such as **1c** and **1d**.

The ^1H NMR spectra were measured in $CDCl_3$ with a 90 MHz instrument. TLC was performed on glass plates precoated with silica gel.

5-(Methylthio)-3,4-dihydro-2*H*-pyran (5)

*By Reaction of **2** with Dimethylmethylmercaptosulfonium Tetrafluoroborate*: To a stirred solution of dimethylmethylmercaptosulfonium tetrafluoroborate (**3**;[3] 5.88 g, 30 mmol) in anhydrous MeCN (50 mL) was added dropwise at –20 °C within 20 min a solution of dihydropyran (**2**; 1.83 mL, 20 mmol) in anhydrous MeCN (20 mL). The stirring at –20 °C was continued for 2.5 h and a solution of *i*-Pr_2NEt (**4**; 38 mmol, 6.6 mL) in MeCN (10 mL) was added within 20 min at –20 °C. After removing the cooling bath, the mixture was warmed up to r.t. overnight and the reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with H_2O (2 × 15 mL). After drying (Na_2SO_4), filtration, and removal of the solvent, the foul smelling residual oil (5.79 g) was distilled in a Kugelrohr apparatus at 80–90 °C/12 mmHg to give pure **5** as a colorless oil; yield: 1.49 g (57%); R_f = 0.68 (toluene–EtOAc, 5:1).

^1H NMR (90 MHz, $CDCl_3$): δ = 6.70 (s, 1 H, =CH), 3.95 [t, *J* = 5 Hz, 2 H, OCH_2], 2.1 (s, 3 H, SCH_3), 1.8–2.3 (m, 4 H, $OCH_2CH_2CH_2$).

Anal. Calcd for $C_6H_{10}OS$ (130.21): C, 55.35; H, 7.74; S, 24.63. Found: C,55.25; H, 7.64; S, 24.16.

*From **2** via the Chloride **8***: To a cooled (–50 °C) solution Me_2S_2 (**6**; 4.45 mL, 50 mmol) in anhydrous CH_2Cl_2 (25 mL) was added a solution of SO_2Cl_2 (4.07 mL, 50 mmol) in anhydrous CH_2Cl_2 (15 mL) with stirring within 10 min. After further 5 min, a solution of dihydropyran (**2**; 9.15 mL, 100 mmol) in CH_2Cl_2 (20 mL) was added with stirring at –50 °C. Subsequently, a solution of DBU (16.1 mL, 110 mmol) in CH_2Cl_2 (25 mL) was added at –50 °C. After warming up to r.t. overnight, the mixture was washed with sat. aq $NaHCO_3$ (2 × 25 mL), the organic phase dried (Na_2SO_4), filtered, and concentrated. Distillation of the crude product in a Kugelrohr apparatus at 80–90 °C/12 mmHg afforded **5** as a colorless oil; yield: 4 g (31%).

*From **2** by Reaction with the S-Oxide **9***: Me_2S_2 (**6**; 8.87 mL, 100 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C and a suspension of 80% *m*-chloroperbenzoic acid (21.56 g, 100 mmol) in CH_2Cl_2 (200 mL) was added within 1 h with stirring. After 5 h additional reaction time at 0 °C, the suspension was filtered and the filtrate dried (Na_2SO_4), and evaporated to give 9.85 g crude *S*-oxide **9**, which was distilled in a Kugelrohr apparatus at 70–90 °C/12 mmHg; yield: 8.2 g (74%). To a solution of the *S*-oxide **9** (1.32 g, 12 mmol) and dihydropyran (**2**; 1.83 mL, 20 mmol) in anhydrous CH_2Cl_2 (25 mL) was added dropwise a solution of trifluoroacetic acid anhydride (1.38 mL, 10 mmol) in CH_2Cl_2 (5 mL) at r.t. with stirring while cooling in a water bath. After 2 h at r.t., a solution of DBU (3.22 mL, 22 mmol) in CH_2Cl_2 (5 mL) was added to the brown reaction mixture, whereupon the dark mixture turned to yellow. After keeping the reaction mixture for 2 d, it was shaken with sat. aq $NaHCO_3$, dried (Na_2SO_4), filtered, and evaporated. The crude product (3.98 g) was distilled in a Kugelrohr apparatus at 80–90 °C/12 mmHg to give pure **5** as a colorless oil; yield: 0.99 g (38%).

5-(Methylsulfonyl)-3,4-dihydro-2*H*-pyran (11)

*By Oxidation of Sulfide **5***: A solution of NaH_2PO_4 (2.07 g 15 mmol) in H_2O (10 mL) was diluted with MeOH (25 mL) and combined with a solution of $KHSO_5$ (6.45 g, 10.5 mmol) in H_2O (30 mL) and cooled to 0 °C. A solution of **5** (0.65 g, 5 mmol) in MeOH (15 mL) was added dropwise with stirring within 1 h and the stirring was continued for 3 h at 0 °C. After warming up to r.t. overnight, H_2O was added to the mixture and extracted with CH_2Cl_2 (5 × 100 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated to give crude **11** (0.55 g, 68%). On extraction of the crude product repeatedly with Et_2O and concentration of the Et_2O, the sulfone **11** crystallized as colorless crystals; yield: 0.45 g (28%); mp 76–77 °C; R_f = 0.34 (EtOAc–MeOH, 8:2).

^1H NMR (90 MHz, $CDCl_3$): δ = 7.48 (s, 1 H, =CH), 4.15 (t, *J* = 5 Hz, 2 H, OCH_2), 2.95 (s, 3 H, SCH_3), 1.80–2.50 (2 m, 4 H, $OCH_2CH_2CH_2$).

Anal. Calcd for $C_6H_{10}O_3S$ (162.21): C, 44.43; H, 6.21; S, 19.77. Found C, 44.33; H, 6.10; S, 19.53.

*By Oxidation of Sulfoxide **12***: To a solution of aq 10% NaOCl (1.5 mL, 2 mmol) and aq 2 N NaOH (0.5 mL, 2 mmol) was added 5-(methylsulfinyl)-3,4-dihydro-2*H*-pyran (**12**; 0.29 g, 2 mmol) and the mixture stirred overnight at r.t. Then, a further amount of aq 10% NaOCl (1 mL) was added and the mixture was kept again overnight, whereupon no starting material **12** could be detected anymore by TLC (eluent: EtOAc–MeOH, 8:2). After the addition of CH_2Cl_2 (50 mL) and a small amount of H_2O, the organic phase was dried (Na_2SO_4), filtered, and evaporated to give crude **11** (0.25 g), which was crystallized from Et_2O to give pure **11** in two crops; yield: 0.15 g (47%); colorless crystals; mp 76–77 °C.

5-(Methylsulfinyl)-3,4-dihydro-2*H*-pyran (12)

To an ice cold stirred solution of **5** (2.6 g, 20 mmol) in MeOH (100 mL) was added dropwise a solution of $NaIO_4$ (4.28 g, 20 mmol) in H_2O (60 mL), whereupon the solution turned yellow and a colorless precipitate formed. After stirring overnight at r.t., the mixture was filtered, and the filtrate concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL), dried (Na_2SO_4), and evaporated to give the crude oily racemic **12** (2.88 g). Distillation at 120 °C/600 mmHg afforded purified **12** as a colorless oil; yield: 2.23 g (76%).

^1H NMR (90 MHz, $CDCl_3$): δ = 7.50 (s, 1 H, =CH), 4.10 (t, *J* = 6 Hz, 2 H, OCH_2), 2.90 (s, 3 H, SCH_3), 1.80–2.50 (2 m, 4 H, $OCH_2CH_2CH_2$).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380217.

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