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ASYMMETRIC SYNTHESIS OF THE SULFOXIDE METABOLITE OF ON-579 BY THE KAGAN PROTOCOL

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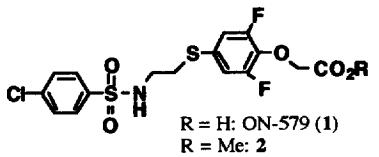
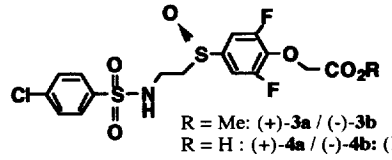
Abstract: A synthesis of both enantiomers of bio-active metabolite of ON-579; 4-[2-(4-chlorophenyl-sulfonylamino)-ethylsulfinyl]-2,6-difluorophnoxyacetic acid was accomplished by the asymmetric oxidation of ON-579 methyl ester followed by hydrolysis. Difference in TXA_2 receptor antagonizing activity was noted for the enantiomers in an U46619-induced rabbit platelet aggregation inhibitory activity. © 1997 Elsevier Science Ltd.

ON-579 (**1**) is a potent and selective non-prostanoid TXA_2 receptor antagonist, which has been investigated as a clinical candidate for asthma.[1] During the pharmacokinetical studies of ON-579, the sulfoxide **M-2** (**4a** and/or **4b**) was found to be the major and bio-active metabolite in animal urine. A method for preparation of a quantitative amount of each enantiomer of **M-2** was required for pharmacokinetical, and toxicological studies as a part of the further development of ON-579.



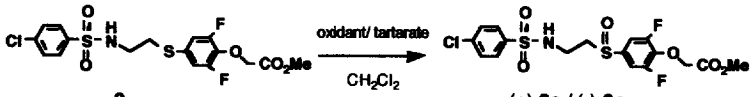
R = H: ON-579 (**1**)
R = Me: **2**



R = Me: (+)-**3a** / (-)-**3b**
R = H : (+)-**4a** / (-)-**4b**: **(M-2)**

Asymmetric oxidation of achiral ON-579 methyl ester (**2**) was accomplished by Kagan's method, with conditions reported for thioanisole derivatives.[2,3] At first, oxidation of **2** was examined by treatment with 1.1 equivalent of *tert*-butyl hydroperoxide (TBHP) in the presence of one equivalent of water and (+)-diethyl tartarate (DET) as an asymmetric ligand at -23 ℃ in CH_2Cl_2 (entry 1) to give *d*-sulfoxide (**3a**) in a fair chemical yield, but the enantioselectivity was relatively low (*ee*[4] = 56%). However, the enantioselectivity of the resulting sulfoxide was reported to be generally low with rather bulky alkyl-arylsulfide such as **2**.[2,3] Optimization of the reaction conditions was examined for preparation of the sulfoxide with good optical purity, since Di Furia *et al.* commented that the effects of the reaction parameters on the optical yields does not follow a simple pattern.[5] The species of the oxidizing agent and the chiral tartarate, and the molar ratio of them were varied [3,6] and the results were illustrated in Table 1.

Table 1



2 (+)-**3a** / (-)-**3a**

Entry	oxidant	(eq)	tartarate	(eq)	Ti(*i*PrO)$_4$ (eq)	H_2O (eq)	temp (℃)	time (hr)	Yield (%)	*d/l*	*ee*[a] (%)
1	TBHP[b]	(1.1)	(+)-DET[c]	(2.0)	1.0	1.0	-23	16	65.0	*d*	56
2	TBHP	(1.1)	(+)-DIPT[d]	(2.0)	1.0	1.0	-23	16	63.7	*d*	23
3	CHP[e]	(1.0)	(+)-DET	(0.5)	0.5	0.5	-23	40	72.6	*d*	57
4	CHP	(1.0)	(+)-DIPT	(1.0)	0.5	0.5	-23	16	69.2	*d*	36
5	CHP	(1.0)	(+)-DET	(2.0)	1.0	1.0	-23	16	79.0	*d*	55
6	CHP	(1.0)	(+)-DET	(2.0)	1.0	–[f]	-23	3.5	37.6	*l*	9[g]
7	CHP	(1.0)	(+)-DET	(1.0)	0.5	0.5	-23	3	59.2	*d*	82
8	TBHP	(1.0)	(+)-DET	(1.0)	0.5	0.5	-23	5	52.0	*d*	27
9	CHP	(1.0)	(+)-DET	(1.0)	0.1	0.1	-23	5	35.8	*d*	18
10[h]	CHP	(1.0)	(+)-DET	(1.0)	0.5	0.5	-23	5	29.3	*d*	23
11	CHP	(1.0)	(+)-DET	(1.0)	0.5	0.5	0	4	42.9	*d*	22
12	CHP	(1.0)	(+)-DET	(1.0)	0.5[i]	0.5	-23	5	75.1	*dl*	0
13	CHP	(1.0)	(-)-DET	(1.0)	0.5	0.5	-23	3	58.3	*l*	73

[a]determined by HPLC, [b]*tert*-butyl hydroperoxide, [c](+)-diethyl tartarate, [d](+)-diisopropyl tartarate, [e]cumene hydroperoxide, [f]performed in the presence of MS4A, [g](-)-**3a** was obtained, [h]performed in $ClCH_2CH_2Cl$. [i]MoO_2acac_2 was used instead of Ti(*i*PrO)$_4$,

Among the reaction conditions examined, the condition of entry 7 (**2**/ CHP/ (+)-DET/ Ti(*i*PrO)$_4$/ H_2O = 1.0/ 1.0/ 1.0/ 0.5/ 0.5) gave the best result. Chiral sulfoxide **3a** was obtained in a fair optical yield (*ee*: 82%) with moderate chemical yield (Y: 59%). Oxidation at 0 ℃ (entry 11) and with TBHP at -23 ℃ (entry 8) reduced enantioselectivity. Reaction in dichloroethane (entry 10) and with lower amounts of titanium complex (entry 9) led to reduced enantioselecivity and chemical yields. Use of other Lewis acid such as MoO_2acac_2[5] gave racemic sulfoxide in good chemical yield (entry 12).

Optical purity of **3a** was enriched by fractional recrystallization from EtOAc (*ee*: 95.6%, chemical yield: 57%), then **3a** was hydrolyzed with 10% NaOH aq/ MeOH to give (+)-**4a** in 95.7 % *ee* with quantitative chemical yield. The other enantiomer (-)-**4b** was obtained in 94.4% *ee* by the same way using (-)-DET as the chiral tartarate (entry 13).[7]

However, the absolute configurations of (+)-**4a** and (-)-**4b** have not been confirmed because any crystals suitable for X-ray analysis were not obtained, they were assigned to be *R* and *S* based on the experimental rule for alkyl- arylsulfide.[6]

U46619-induced rabbit platelet aggregation inhibitory activities of the chiral sulfoxide (+)-**4a**, (-)-**4b** and the racemate (±)-**4** along with **1** were tested to uncover the difference between the enantiomers for its TXA_2 receptor antagonizing ability. The IC_{50} value of (+)-**4a**, (-)-**4b**, (±)-**4** and **1** were ≥100, 13.3±0.9, 18.9±1.2 and 0.34±0.07x10^{-6}M respectively.[8] These results suggest that (-)-**4b** may contribute *in vivo* biological activity of **1**.

Typical Experimental Procedure: To a solution of (+)-DET (5.35 ml, 30 mmol) in CH_2Cl_2 (130 ml) was added successively Ti(*i*PrO)$_4$ (4.48 ml, 15 mmol) and H_2O (0.18 ml, 15 mmol) at 18 ℃ under argon atmosphere. After stirred for 25 minutes at room temperature, a solution of **2** (13.56g, 30 mmol) in CH_2Cl_2 (30 ml) was added to the reaction mixture. The solution was cooled to -30℃, then cumene hydroperoxide (80% in toluene, 5.54 ml, 30 mmol) was added thereto and stirred for 3 h at -23 ℃. After addition of H_2O (5 ml), the reaction mixture was stirred vigorously for 2h at room temperature, then filtered through celite. Organic layer was separated, dried over $MgSO_4$, evaporated *in vacuo* to give crude product, which was purified by flash chromatography (SiO_2, EtoAc:hexane = 50:50 to 100:0) to give (+)-**3a** (8.3g, Y: 59.2%, *ee:* 82%) and **2** (5.1 g, 37.6 %). Fractional recrystallization of (+)-**3a** from EtOAc and toluene gave optically enriched (+)-**3a** (4.69 g, ee: 95.6%). mp: 112–114.5 ℃. $[\alpha]_D$ (c: 1.00%, $CHCl_3$): +182.5°.

(+)-**3a** was hydrolyzed by 10% NaOH in MeOH and recrystallized from EtOAc/ hexane to give (+)-**4a** (Y: 98.7 %, ee: 95.7 %) as a colorless powder. mp: 134.5–136.5 ℃. $[\alpha]_D$ (c: 1.05%, acetone): +129°. *Anal* Calcd for $C_{16}H_{14}NO_6S_2F_2Cl$: C, 42.34; H, 3.11; N, 3.09; F, 8.37; Cl, 7.81; S, 14.13. Found: C, 42.14; H, 2.93; N, 3.08; F, 7.89; Cl, 7.80; S, 14.32.

References and Notes:

1) Sato, M.; Kawashima, Y.; Goto, J.; Yamane, Y.; Chiba, Y.; Jinno, S.; Satake, M.; Iwata, C. *Eur. J. Med. Chem.* **1995**, *30*, 403.

2) Pitchen, P.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 1049.

3) Pitchen ,P.; Dunach, E.; Dashmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188.

4) Enantiomeric excess of each compound was determined by HPLC method with a chiral column CHIRALPAK AS (Daisel) (0.46ϕx 25 cm) at 27 ℃ detected with UV at 254 nm using the following elute; 0.1% Et_2NH / EtOH 0.5 ml/ min for (+)-**3a** and (-)-**3b**, and 0.1% CF_3CO_2H / EtOH 0.5ml/ min for (+)-**4a** and (-)-**4b**.

5) Di-Furia, F.; Modena, G.; Serglia, R. *Synthesis* **1984**, 325.

6) Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135.

7) (-)-**3b:** mp: 112.5–113.5 ℃ (toluene). *ee*: 94.0% (HPLC). $[\alpha]_D$ (c: 0.114%, $CHCl_3$): -191°.

(-)-**4b:** mp:135.5–137 ℃ (EtOAc-hexane). *ee*: 94.4% (HPLC). $[\alpha]_D$ (c:1.04%, acetone): -152°. *Anal.* Calcd for $C_{16}H_{14}NO_6S_2F_2Cl$: C, 42.34; H, 3.11; N, 3.09; F, 8.37; Cl, 7.81; S, 14.13. Found: C, 42.25; H, 2.94; N, 3.13; F, 8.36; Cl, 7.70; S, 13.85.

8) The IC_{50} values (mean±SEM) were calculated by regression analysis from the four dose groups with four different predictions by U-46619 (5 μM)-induced rabbit platelete aggregation tests.

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