Synthesis of a Novel Dual Inhibitor of Thromboxane A_2 Synthetase and 5-Lipoxygenase (E3040) *via* the Direct Coupling Reaction of Hydroquinone with 3-Pyridinecarboxaldehyde

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Synthesis of a novel dual inhibitor of thromboxane A_2 synthetase and 5-lipoxygenase, 5,7-dimethyl-6-hydroxy-2-methylamino-4-(3-pyridylmethyl)benzothiazole (E3040), was accomplished *via* a new coupling reaction, in which a key intermediate, (3,6-dihydroxy-2,4-dimethylphenyl)-(3-pyridyl)methanol, was easily synthesized in a high yield from 2,6-dimethyl-1,4-benzohydroquinone and 3-pyridinecarboxaldehyde in 6 N hydrochloric acid. The regio isomers of 3-pyridinecarboxaldehyde also gave the corresponding coupling products in high yields.

Key words dual inhibitor; thromboxane A_2 synthetase; 5-lipoxygenase; direct coupling reaction; 2,6-dimethyl-1,4-benzohydroquinone; pyridinecarboxaldehyde

5,7-Dimethyl-6-hydroxy-2-methylamino-4-(3-pyridylmethyl)benzothiazole (**1**) (E3040), a novel dual inhibitor of thromboxane A_2 synthetase and 5-lipoxygenase, is under development as a candidate antiinflammatory agent for the treatment of inflammatory bowel disease.[1] The previous synthetic method of **1** involves many steps and is costly, owing to the use of the Grignard reaction and CAN (ceric ammonium nitrate) oxidation.[1]

In this report we disclose an efficient, economic and scalable synthesis of **1** *via* the direct coupling reaction of 2,6-dimethyl-1,4-benzohydroquinone (**3**)[2] with 3-pyridinecarboxaldehyde (**4b**). Retrosynthetic analysis indicated that the target compound **1** could be prepared from 3,5-dimethyl-2-(3-pyridylmethyl)-1,4-benzohydroquinone (**2a**) or the hydroxy compound **2b**, which in turn could be derived by the coupling reaction of the hydroquinone **3** with 3-pyridinemethanol (**4a**) or the aldehyde **4b** as shown in Chart 1. We concentrated our efforts on the synthesis of **2a** or **2b**. The facile synthesis of a pyridylmethylhydroquinone such as **2a** or **2b** is of great synthetic importance in the chemistry of biologically active molecules since such compounds can serve as precursors to medicinally useful heterocyclic skeletons.[3] Terao and Nishikawa reported the coupling reaction of secondary 3-pyridinemethanol with trimethyl-1,4-benzohydroquinone in toluene or dichloromethane in the presence of sulfuric acid or trifluoromethanesulfonic acid.[4] But the reaction of the primary alcohol **4a** with the hydroquinone **3** by this method did not give the desired compound **2a**. We tried to use the dimethylacetal **5c**[5] of **4b** instead of **4a** for this coupling. The dimethylacetal **5c** and the hydroquinone **3** were refluxed in methanol in the presence of sulfuric acid to give the desired compound **2c**, as shown in Table 1 (run 2). The substituent R3 of the starting material **5** was adopted corresponding to the alcohol used as the solvent in the reaction in the product **2** and the yields tended to increase with the boiling point of the alcohol (runs 2, 3, 4). But the coupling reaction did not proceed in aprotic solvent (run 1) or *tert*-butyl alcohol (run 5), and also the diacetate **5f**[6] did not afford the desired compound (run 7). The diisopropyl acetal **5e**[7] gave **2e** in the same yield as run 4 in isopropyl alcohol (run 6).

Although this method is a new one, it seemed to be inadequate from the viewpoint of the chemical yields. We attempted to get **2** from the aldehyde **4b** directly in a one-pot reaction, since both the acetalization of **4b** and the following coupling reaction of the acetal **5** with the hydroquinone **3** proceeded under acidic conditions. Thus, the addition of the aldehyde **4b** to isopropyl alcohol containing HCl under ice-water cooling followed by the hydroquinone **3** at the same temperature afforded the corresponding alcohol **2b** in 20% yield, besides the desired compound **2e** (58% yield). This result shows that the alcohol **2b** could be directly obtained from **4b** and **3** under acidic conditions. We performed this coupling reaction of **4b** with **3** in 2, 4, 6 N, or concentrated hydrochloric acid at room temperature, as shown in Table 2 (runs 1, 2, 3, 4). This direct coupling reaction gave the desired compound **2b** under these conditions, in high yields in 4 and 6 N hydrochloric acid and in moderate yields in 2 N and concentrated hydrochloric acid. Interestingly, the reaction

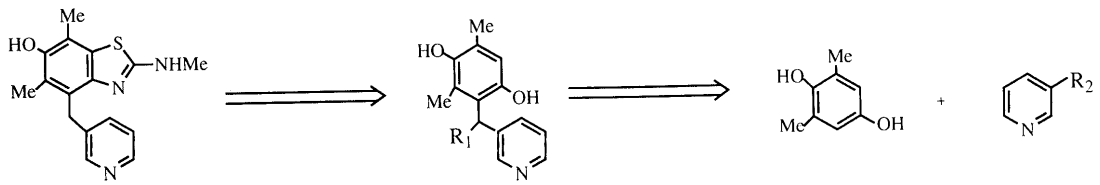

Chart 1

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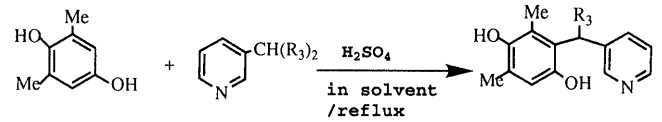
Table 1. Reaction of **3** with **5** in the Presence of Sulfuric Acid in Various Solvents



3

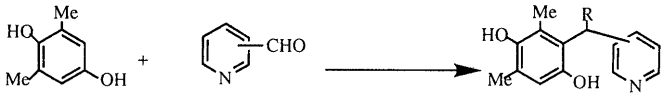
5c: R_3=OMe
5e: R_3=O-iso-Pr
5f: R_3=OAc

2c: R_3=OMe
2d: R_3=OEt
2e: R_3=O-iso-Pr

Run	5	Solvent[a]	Reflux (h)	Product[b]	Yield (%)
1	**5c**	DCM	3	NR	—
2	**5c**	MeOH	50	**2c**	16
3	**5c**	EtOH	18	**2d**	38
4	**5c**	IPA	21	**2e**	58
5	**5c**	*tert*-BuOH	38	NR	—
6	**5e**	IPA	17	**2e**	58
7	**5f**	MeOH	5	NR	—

a) DCM, dichloromethane; IPA, isopropyl alcohol. *b*) NR, no reaction.

Table 2. Reaction of **3** with **4** in Hydrochloric Acid



3

4b: 3-pyridine
4f: 2-pyridine
4g: 4-pyridine

2b: R=OH, 3-pyridine
2c: R=OMe, 3-pyridine
2f: R=OH, 2-pyridine
2g: R=OH, 4-pyridine

Run	4	Reaction conditions	Product(s)	Yield(s) (%)
1	**4b**	2 N HCl/RT/44 h	**2b**	41
2	**4b**	4 N HCl/RT/44 h	**2b**	75
3	**4b**	6 N HCl/RT/17 h	**2b**	91
4	**4b**	Conc. HCl/RT/2 h	**2b**	34
5	**4b**	6 N HCl–MeOH/RT/22 h	**2b**, **2c**	34, 43
6	**4f**	6 N HCl/RT/37 h	**2f**	92
7	**4g**	6 N HCl/RT/17 h	**2g**	93

RT; room temperature.

of **4b** with **3** in a solution of 6 N hydrochloric acid and methanol gave **2b** and **2c** (run 5). Isomers of **4b**, 2- and 4-pyridinealdehyde (**4f**, **4g**) also gave the alcohols **2f** and **2g** in high yields, respectively (runs 6, 7). We have examined the generality of this new coupling reaction, and will present the results elsewhere.[8]

The coupling product **2b** was easily oxidized with nitric acid instead of CAN to afford the corresponding quinone **8** in 90% yield (Chart 2). The quinone **8** was reacted with methylthiourea according to the method of Lau and Gompf[9] to give the benzothiazole **9** in 80% yield. The hydroxy group of the benzothiazole **9** was removed with zinc powder in acetic acid to afford the desired compound **1** (E3040) in 82% yield.

In conclusion, a facile synthesis of the dual inhibitor **1** (E3040) was accomplished *via* a new coupling reaction of 2,6-dimethyl-1,4-benzohydroquinone (**3**) with 3-pyridinecarboxaldehyde (**4b**).

Experimental

Reagents and solvents were purchased from usual commercial sources. Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian Unity 400 (400 MHz) spectrometer. Chemical shifts are given in ppm using tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, br=broad, m=multiplet. Column chromatography was performed on silica gel (Merck, particle size 0.040—0.063 mm). Mass spectra (MS) were obtained on a JEOL JMS-HX100 mass spectrometer. Elemental analyses were performed at the Analytical Chemistry Section of Eisai Tsukuba Research Laboratories.

Reaction of 2,6-Dimethyl-1,4-benzohydroquinone (3) with 3-Pyridinecarboxaldehyde Dimethyl Acetal (5c) in Methanol in the Presence of Sulfuric Acid A solution of **3** (1000 mg, 7.24 mmol), **5c** (1100 mg, 7.24 mmol), and concentrated H_2SO_4 (0.77 ml) in MeOH (15 ml) was refluxed for 50 h and evaporated under reduced pressure. The residue was diluted with water, neutralized with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$, and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane: AcOEt=2:1) to give 3,5-dimethyl-2-(methoxy-3-pyridylmethyl)-1,4-benzohydroquinone (**2c**) (300 mg, 16%) as an oil. MS *m/z*: 260 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s), 2.23 (3H, s), 3.52 (3H, s), 5.70 (1H, s), 6.60 (1H, s), 7.25 (1H, dd, J=8.0, 5.2 Hz), 7.65 (1H, d, J=8.0 Hz), 7.95 (1H, s), 8.75 (1H, d, J=5.2 Hz), 8.55 (1H, br). Compound **2c** was converted to the HCl salt with HCl–AcOEt. mp 177—178 °C (CH_3CN).

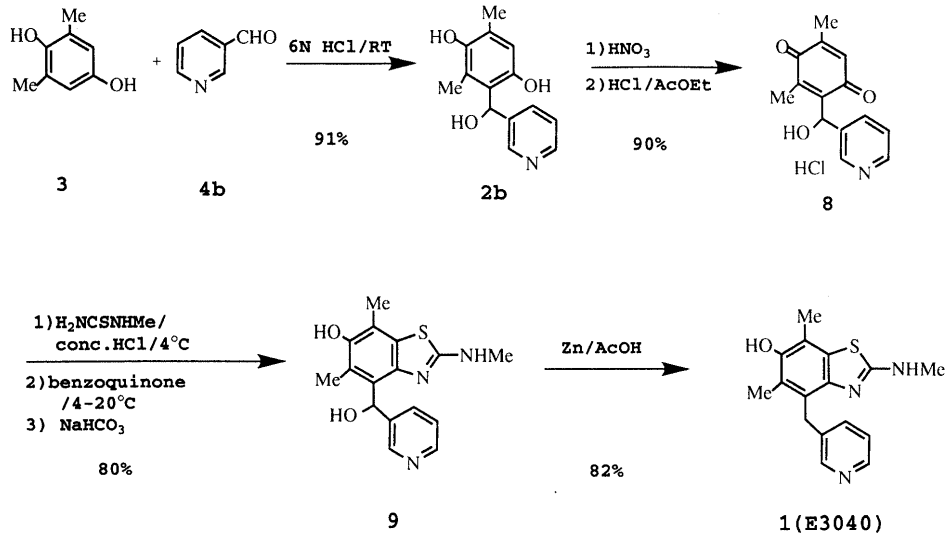


Chart 2

Anal. Calcd for $C_{15}H_{17}NO_3 \cdot HCl$: C, 60.91; H, 6.13; N, 4.74. Found: C, 60.65; H, 6.15; N, 4.75.

Reaction of 3 with 5c in Ethanol in the Presence of Sulfuric Acid A solution of **3** (500 mg, 3.62 mmol), **5c** (554 mg, 3.62 mmol), and concentrated H_2SO_4 (0.3 ml) in EtOH (7.5 ml) was refluxed for 18 h. The reaction mixture was treated as described for the preparation of **2c** to afford 3,5-dimethyl-2-(ethoxy-3-pyridylmethyl)-1,4-benzohydroquinone (**2d**) as an oil (370 mg, 38%). MS *m/z*: 274 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=6.8 Hz), 2.14 (3H, s), 2.22 (3H, s), 3.6—3.8 (3H, m), 5.78 (1H, s), 6.60 (1H, s), 7.23 (1H, J=8.0, 4.8 Hz), 8.63 (1H, d, J=8.0 Hz), 8.13 (s, 1H), 8.51 (1H, d, J=4.8 Hz), 8.57 (1H, s). HCl salt of **2d**: mp 185—187 °C (CH_3CN). *Anal.* Calcd for $C_{16}H_{19}NO_3 \cdot HCl$: C, 62.03; H, 6.51; N, 4.52. Found: C, 61.96; H, 6.59; N, 4.56.

Reaction of 3 with 5c in Isopropyl Alcohol in the Presence of Sulfuric Acid A solution of **3** (500 mg, 3.62 mmol), **5c** (554 mg, 3.62 mmol), and concentrated H_2SO_4 (0.3 ml) in isopropyl alcohol (7.5 ml) was refluxed for 21 h. The reaction mixture was treated as usual to afford 3,5-dimethyl-2-(isopropoxy-3-pyridylmethyl)-1,4-benzohydroquinone (**2e**) as an oil (602 mg, 58%). MS *m/z*: 287 (MH^+). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=6.0 Hz), 1.32 (3H, d, J=6.0 Hz), 2.15 (3H, s), 2.22 (3H, s), 3.88 (1H, hept, J=6.0 Hz), 5.89 (1H, s), 6.60 (1H, s), 7.22 (1H, dd, J=8.0, 4.8 Hz), 7.58 (1H, d, J=8.0 Hz), 8.18 (1H, s), 8.50 (1H, d, J=4.8 Hz). HCl salt of **2e**: mp 171—173 °C (CH_3CN). *Anal.* Calcd for $C_{17}H_{21}NO_3 \cdot HCl$: C, 63.06; H, 6.85; N, 4.33. Found: C, 62.96; H, 6.74; N, 4.34.

Reaction of 3 with 3-Pyridinecarboxaldehyde Diisopropyl Acetal (5e) in Isopropyl Alcohol in the Presence of Sulfuric Acid A solution of **3** (3.07 g, 22.2 mmol), **5e** (3.40 g, 16.2 mmol), and concentrated H_2SO_4 (1.8 ml) in isopropyl alcohol (45 ml) was refluxed for 17 h. The reaction mixture was treated as usual to afford **2e** as an oil (2.71 g, 58%). Analytical data were identical with those of an authentic sample.

One-Pot Reaction of 3 with 3-Pyridinecarboxaldehyde (4b) Dry HCl was passed into a stirred solution of **4b** (1.5 g, 14.0 mmol) in isopropyl alcohol (15 ml) under cooling with ice-water for 30 min, and then the mixture was stirred for 30 min at the same temperature, followed by 30 min at room temperature. After addition of a solution of **3** (2.13 g, 15.4 mmol) in isopropyl alcohol (10 ml) to the mixture at −10 °C over a period of 5 min, the reaction mixture was stirred at 4 °C for 88 h and then treated as usual to afford **2e** (2.35 g, 58%) as an oil and (3,6-dihydroxy-2,4-dimethylphenyl)-(3-pyridyl)methanol (**2b**) (0.69 g, 20%) as a white solid. Analytical data of **2e** were identical with those of an authentic sample. **2b**: mp: 181—183 °C. MS *m/z*: 246 (MH^+). *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.56, H, 6.16; N, 5.71. Found: C, 68.32; H, 6.19; N, 5.45. ^{1}H-NMR (DMSO-d_6) δ: 1.91 (3H, s), 2.07 (3H, s), 6.12 (1H, br), 6.28 (1H, s), 6.45 (1H, s), 7.27 (1H, dd, J=4.0, 8.0 Hz), 7.40 (1H, br), 7.57 (1H, d, J=8.0 Hz), 8.36 (1H, d, J=4.0 Hz), 8.42 (1H, s), 8.90 (1H, br).

Reaction of 3 with 4b in 6 N Hydrochloric Acid A solution of **3** (25 g, 0.18 mol) and **4b** (16 g, 0.15 mol) in 6 N hydrochloric acid (200 ml) was stirred at room temperature for 17 h. The reaction mixture was diluted with H_2O (300 ml) and AcOEt (25 ml), neutralized with $NaHCO_3$ (111 g), and then stirred for 10 min. The precipitate was collected by filtration and washed with H_2O, AcOEt, then isopropyl ether. This precipitate was dried under reduced pressure to give **2b** (33 g, 91%). Analytical data were identical with those of an authentic sample.

Reaction of 3 with 2-Pyridinecarboxaldehyde (4f) in 6 N Hydrochloric Acid A solution of **3** (1.59 g, 11.5 mmol) and **4f** (1.12 g, 10.5 mmol) in 6 N hydrochloric acid (8 ml) was treated according to a similar procedure to that described for **4b**, to give (3,6-dihydroxy-2,4-dimethylphenyl)-(2-pyridyl)methanol (**2f**) (2.37 g, 92%). mp 160—161 °C. MS *m/z*: 245 (M^+). *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.57; H, 6.14; N, 5.72. ^{1}H-NMR (DMSO-d_6) δ: 1.96 (3H, s), 2.04 (3H, s), 6.20 (1H, br), 6.13 (1H, s), 6.37 (1H, s), 7.19 (1H, dd, J=4.8, 8.0 Hz), 7.35 (1H, br), 7.48 (1H, d, J=8.0 Hz), 7.73 (1H, ddd, J=1.8, 8.0, 8.0 Hz), 8.41 (1H, dd, J=1.8, 4.8 Hz), 8.95 (1H, br).

Reaction of 3 with 4-Pyridinecarboxaldehyde (4g) in 6 N Hydrochloric Acid A solution of **3** (1.59 g, 11.5 mmol) and **4g** (1.12 g, 10.5 mmol) in 6 N hydrochloric acid (8 ml) was similarly treated to give (3,6-dihydroxy-2,4-dimethylphenyl)-(4-pyridyl)methanol (**2g**) (2.40 g, 93%). mp 158—159 °C. MS *m/z*: 246 (MH^+). *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.52; H, 6.17; N, 5.66. ^{1}H-NMR (DMSO-d_6) δ: 1.88 (3H, s), 2.06 (3H, s), 5.98 (1H, br), 6.25 (1H, s), 6.45 (1H, s), 7.20 (2H, d, J=6.0 Hz), 7.38 (1H, br), 8.41 (2H, d, J=6.0 Hz).

3,5-Dimethyl-2-(hydroxy-3-pyridylmethyl)-1,4-benzoquinone Hydrochloride (8) Concentrated HNO_3 (78 ml) was added to a solution of **2b** (30 g, 0.12 mol) in H_2O (60 ml) and tetrahydrofuran (60 ml) under cooling with ice-water over a period of 15 min and stirring was continued for 5 min. The reaction mixture was diluted with AcOEt (450 ml)–H_2O (60 ml), and then neutralized with $NaHCO_3$. The organic layer was separated, washed with water and dried over $MgSO_4$, then 4 N HCl–AcOEt was added under cooling with ice-water. The precipitate was collected by filtration, washed with AcOEt and isopropyl ether, then dried under reduced pressure to give **8** (30.4 g, 90%). mp 155—160 °C. MS *m/z*: 244 (MH^+). ^{1}H-NMR (DMSO-d_6) δ: 1.97 (3H, d, J=1.6 Hz), 1.98 (3H, s), 6.68 (1H, q, J=1.6 Hz), 7.95 (1H, dd, J=5.6, 8.0 Hz), 8.40 (1H, d, J=8.0 Hz), 8.76 (1H, s), 8.77 (1H, d, J=5.6 Hz).

[4-(5,7-Dimethyl-6-hydroxy-2-methylamino)benzothiazolyl]-(3-pyridyl)methanol (9) A mixture of **8** (30 g, 0.11 mol) and methylthiourea (9.68 g, 0.11 mol) in a solution of EtOH (300 ml) and concentrated HCl (21.7 ml) was stirred at 4 °C for 15 h. After addition of AcOEt (300 ml) to the reaction mixture, the precipitate was collected by filtration, and washed with AcOEt, followed by isopropyl ether. A solution of 1,4-benzoquinone (2.9 g, 27 mmol) in tetrahydrofuran (24 ml) was added to a suspension of this precipitate in EtOH (300 ml) under cooling with ice-water. The mixture was stirred at 4 °C for 4 h and then at 20 °C for 3 h. After addition of AcOEt (200 ml) to the mixture, the precipitate was collected by filtration, and washed with AcOEt, followed by isopropyl ether to give the hydrochloride (36.3 g). The hydrochloride was dissolved in H_2O (524 ml) and AcOEt (145 ml), and the mixture was neutralized with $NaHCO_3$. The precipitate was collected by filtration, washed with AcOEt and isopropyl ether, and then dried under reduced pressure to give **9** (26.9 g, 80%). mp 201—203 °C. MS *m/z*: 316 (MH^+). ^{1}H-NMR (DMSO-d_6) δ: 2.03 (3H, s), 2.21 (3H, s), 2.88 (3H, d, J=4.8 Hz), 6.51 (1H, d, J=6.6 Hz), 6.55 (1H, d, J=6.6 Hz), 7.27 (1H, dd, J=4.8, 8.0 Hz), 7.60 (1H, d, J=8.0 Hz), 7.82 (1H, q, J=4.8 Hz), 7.97 (1H, s), 8.35 (1H, d, J=4.8 Hz), 8.46 (1H, s).

5,7-Dimethyl-6-hydroxy-2-(methylamino)-4-(3-pyridylmethyl)benzothiazole (1, E3040) Zinc powder (2.6 g, 39.8 mmol) was added to a solution of **9** (5.0 g, 15.9 mmol) in AcOH (50 ml), and the mixture was refluxed for 26 h, then filtered. The filtrate was diluted with AcOEt (200 ml) and then stirred under cooling with ice-water for 10 min. The precipitate was collected by filtration, and dissolved in a mixture of H_2O (50 ml) and 5 N HCl (4 ml). This solution was filtered, and the filtrate was neutralized with saturated aqueous $NaHCO_3$. The precipitate was collected by filtration, washed with H_2O and then dried under reduced pressure to give **1** (3.89 g, 82%). Analytical data were identical with those of an authentic sample.

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