



Synthesis of optically active 2,3-dihydrobenzofuran derivatives through a combination strategy of iron(III)-catalyzed reaction and enzymatic reaction

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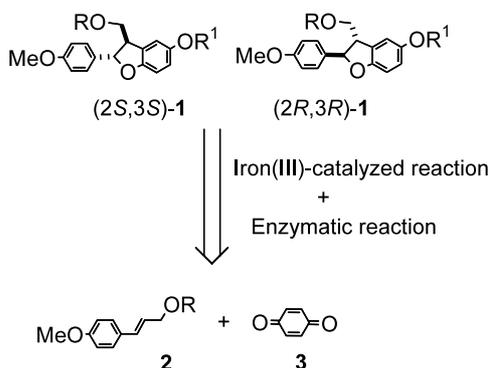
Abstract—Synthesis of optically active 2,3-dihydrofuran derivatives has been accomplished through a combination strategy of ferric ion-catalyzed cycloaddition of styrene derivatives with quinones and following lipase-catalyzed enantioselective acylation. © 2003 Elsevier Science Ltd. All rights reserved.

Iron is recognized as an economical and pollution free metal source.¹ Recently we reported the synthesis of 2,3-dihydrobenzofuran by the reaction of styrene derivatives with 1,4-benzoquinone using alumina-supported iron(III) perchlorate or iron(II) tetrafluoroborate as catalysts,² and we found that the reaction was greatly accelerated in an ionic liquid solvent system.³ Since 2,3-dihydrobenzofuran molecular frame is common in natural compounds,⁴ it was necessary to establish the synthetic route to access optically active form of 2,3-dihydrobenzofuran derivatives. Engler and co-workers reported excellent results in the enantioselective synthesis of 2,3-dihydrobenzofuran derivatives using chiral Lewis acid-catalyzed reaction;⁵ however, a large excess amount of a chiral Titanium-

(IV) complex was required for the reaction.^{5,6} From the standpoint of Green Chemistry, we should develop a greener reaction process through catalytic reaction systems. So, we wanted to synthesize optically active 2,3-dihydrobenzofuran derivatives through a catalytic reaction process. Here we report the successful results of the synthesis of optically pure 2,3-dihydrobenzofuran derivatives using a combination strategy of iron salt-catalyzed reaction and enzymatic reaction as illustrated in Scheme 1.

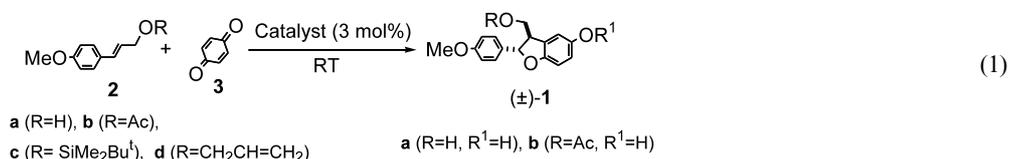
Since iron(III) salt-catalyzed cycloaddition of styrene derivatives with 1,4-benzoquinone was strongly dependent on the nature of these derivatives,² we first tested the cycloaddition reaction using 3-(4-methoxy)phenyl-2-propenol (**2a**) as substrate in the presence of 3 mol% of alumina-supported iron(III) perchlorate in acetonitrile (Eq. (1)). But no desired compound was obtained and starting **2a** was recovered after 24 h reaction as shown in Table 1 (entry 1).

Iron(II) tetrafluoroborate worked very well for the reaction of *trans*-anethol with 1,4-benzoquinone in the [bmim]PF₆ solvent system,⁷ but no desired product was obtained for the reaction of **2a** in this catalytic system either (entry 2). *t*-Butyldimethylsilyl ether **2c** and allylic ether **2d** also gave no desired product (entries 3 and 4) and it was finally found that the hydroxyl group must be protected as acetate; 2-(4-methoxy)phenyl-3-acetoxymethyl-2,3-dihydro-5-benzofuranol (**1b**) was obtained with high *trans* selectivity (11:1) from 3-(4-methoxy)phenyl-2-propenyl acetate (**2b**) in 84% yield (entry 4). The reaction of **2b** using iron(II) tetrafluoroborate as catalyst in [bmim]PF₆ proceeded, but



Scheme 1.

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Table 1. Synthesis of 2-aryl-3-hydroxymethyl-2,3-dihydrobenzofuran derivatives using iron salt-catalyzed reaction

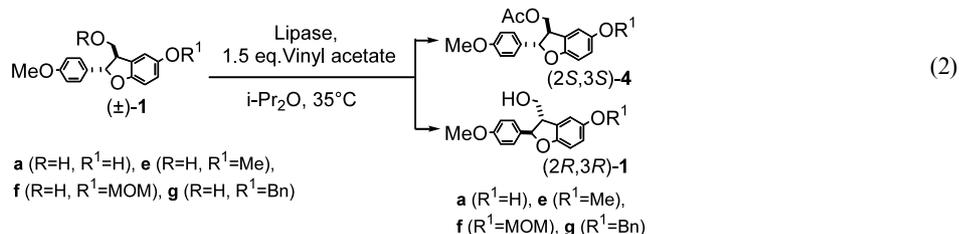
Entry	R	Catalyst	Solvent	Time	Yield (%) ^a	<i>trans/cis</i> ^b
1	H	Fe(ClO ₄) ₃ /Al ₂ O ₃	CH ₃ CN	24 h	0 ^c	–
2	H	Fe(BF ₄) ₂ /6H ₂ O	[bmim]PF ₆	1 h	0 ^c	–
3	SiMe ₂ Bu ^t	Fe(ClO ₄) ₃ /Al ₂ O ₃	CH ₃ CN	48 h	0 ^c	–
4	CH ₂ CH=CH ₂	Fe(ClO ₄) ₃ /Al ₂ O ₃	CH ₃ CN	24 h	0 ^d	–
5	Ac	Fe(ClO ₄) ₃ /Al ₂ O ₃	CH ₃ CN	2 h	84	11:1
6	Ac	Fe(BF ₄) ₂ /6H ₂ O	[bmim]PF ₆	20 min	23	20:1

^a Isolated yield.^b Determined by capillary GC-analysis.^c No reaction took place and starting compound **2** was recovered.^d Unidentified polymeric products were produced but neither desired product **1** nor starting compound **2** was recovered.

the result was insufficient (entry 5). Therefore, alumina-supported iron(III) perchlorate in acetonitrile was appropriate for this type of substrate, while iron(II) catalyst in an ionic solvent system gave better results when *trans*-anethol was used as substrate.²

Next we attempted to prepare optically active 2,3-dihydrobenzofuran by lipase-catalyzed enantioselective transesterification.⁹ Acetate (±)-**1b** was treated with potassium carbonate in methanol to release alcohol (±)-**1a**, which was subjected to the lipase-catalyzed acylation using vinyl acetate as an acyl donor. Enzy-

matic acetylation of (±)-**1a** proceeded smoothly in diisopropyl ether at 35°C (Eq. (2)); however, the best enantioselectivity (*E* value¹⁰) was only 10 when Novozyme 435 was used as catalyst.^{11,12} This was insufficient from a practical aspect. We anticipated that protection of the phenolic hydroxyl group on the C-ring of (±)-**1a** might affect the enantioselectivity of the enzymatic reaction, because the acidic phenol hydroxyl group is assumed to bind with a peptide residue of the enzyme through a hydrogen bond formation; this may cause an incorrect orientation of the large aromatic ring moiety in the active site. Three types of compounds,

Table 2. Synthesis of optically active 2-aryl-3-hydroxymethyl-2,3-dihydrofuran derivatives

Entry	R ¹	Enzyme ^a	Time (h)	Yield of 4 ^b (%) ee ^c	[α] _D of 4 (c ca. 1, CHCl ₃)	Yield of 1 ^b (% ee) ^c	Conv. ^d	<i>E</i> value ^e
1	H	Novozyme	5	21 (78)	–12	38 (21)	0.21	10
2	H	PS	26	33 (45)	–6	57 (35)	0.44	4
3	H	SL	48	18 (65)	–3	54 (22)	0.25	6
4	Me	Novozyme	0.75	47 (91)	–58	32 (79)	0.47	49
5	Me	PS	4	50 (2)	–3	33 (10)	0.85	1
6	Me	MY	10	13 (82)	+51	69 (38)	0.32	15
7	Me	QL	3	28 (8)	+1	64 (13)	0.64	1
8	MOM	Novozyme	1	25 (64)	–28	60 (>99) ^f	0.61	>100
9	Bn	Novozyme	2	40 (>99) ^f	–36	50 (69)	0.41	>400

^a See reference section.^b Isolated yield.^c Enantiomeric excess was determined by HPLC analysis (Daicel ChiralpakOD, hexane/*i*-PrOH = 8:1 or 20:1, 1.0 ml/min).^d conv. (*c*) was calculated by the following formula: $c = eeS / (eeS + eeP)$.¹⁰^e $E = \ln[1 - c(1 + eeP)] / \ln[1 - c(1 - eeP)]$, here *c* means conv.^f Only one enantiomer was detected by HPLC analysis.

5-methoxybenzofuran (\pm)-**1e**,⁸ 5-methoxymethylbenzofuran (\pm)-**1f**, and 5-benzyloxybenzofuran (\pm)-**1g** were prepared,¹³ and subjected to enzymatic transesterification (Eq. (2)). As we anticipated, remarkable enhancement in enantioselectivity was accomplished using these three substrates in the enzymatic transesterification (Table 2).

Practical optical resolution was thus realized when methoxy derivative (\pm)-**1e**, methoxymethyl derivative (\pm)-**1f**, or benzyloxy derivative (\pm)-**1g** was used as substrate. The lipase-catalyzed acylation worked very well with the preference of the (2*S*,3*S*)-enantiomer,¹⁷ and the *E* values almost reached a sufficient level (entries 4, 8, and 9). Remarkable acceleration was also achieved when 5-methoxy derivative (\pm)-**1e** was subjected to the Novozyme-catalyzed reaction, and acetate (2*S*,3*S*)-**4e** was obtained in 47% yield with 91% ee after just 0.75 h (entry 4), while it took 5 h when (\pm)-**1a** was subjected to the reaction (entry 1). It should be emphasized that perfect enantioselective reaction was accomplished when benzyl protected (\pm)-**1g** was used as a substrate; enantiomerically pure (>99% ee) acetate (2*S*,3*S*)-**4g** was obtained in 40% (80% theoretical yield) yield after 2 h reaction at rt (entry 9). In the case of lipase PS-catalyzed reaction, no enhancement in enantioselectivity was recorded by protection of the phenolic hydroxyl group at the 5 position, although remarkable acceleration in the acylation was achieved (entry 5). Lipase MY was the second choice of this reaction among tested enzymes, though this enzyme has an opposite enantiomer preference for this substrate and (2*R*,3*R*)-**4e** was produced by lipase MY-catalyzed reaction (entry 6).

It was very interesting that enantioselectivity of the enzymatic reaction was strongly influenced by the substituent apart from the reaction point in the substrate. We are now assuming that protection of the 5-hydroxyl group is responsible for orienting the aromatic group in the incorrect cavity in the active site.¹⁸ We tend to focus only on the functional groups located near to the reaction point in designing a suitable substrate molecule for the enzymatic reaction. However, the present results suggest there is a possibility of improving enantioselectivity of the enzymatic reaction by proper modification of the substrate, even if the original reaction was inadequate one.

In conclusion, we accomplished the synthesis of optically active 2,3-dihydrobenzofuran derivatives through a combination strategy of ferric iron-catalyzed reaction and enzymatic reaction. It should be noted that the enantioselectivity of lipase-catalyzed reaction was remarkably modified by protecting the phenolic hydroxyl group on the C-ring which is located apart from the reaction point. Further investigation of the scope and limitations of this reaction will make it even more beneficial.

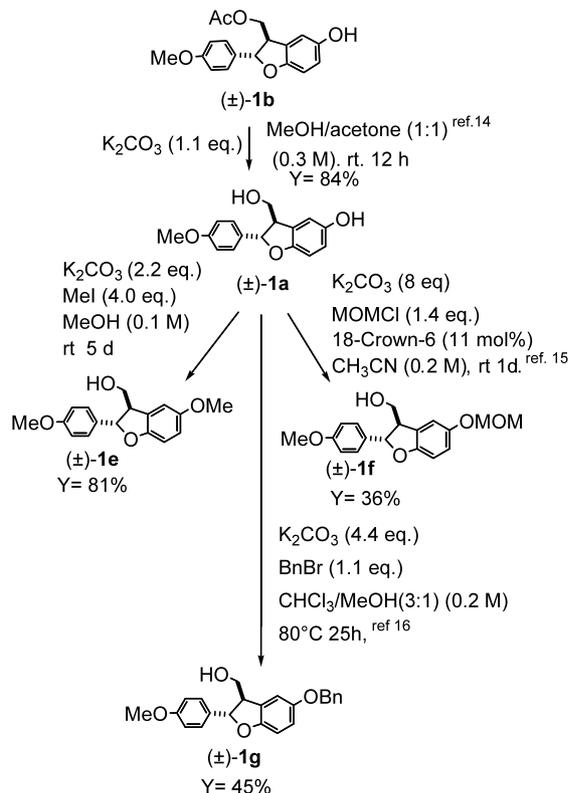
Acknowledgements

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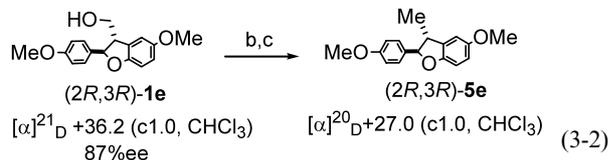
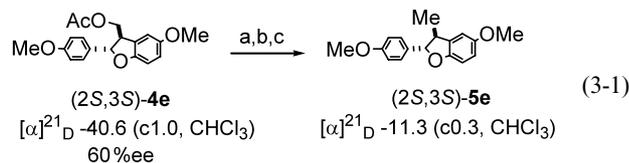
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- Typical experimental procedure for preparing (\pm)-**1e**: To a solution of 3-(4-methoxy)phenyl-2-propene-1-yl acetate (1.14 g, 5.5 mmol) and 1,4-benzoquinone (654 mg, 6.05 mmol) in dry-acetonitrile (1.65 ml) was added Fe(ClO₃)/Al₂O₃ (625 mg, 0.06 equiv.) in one portion, and the mixture was stirred at rt for 1 h, then filtered through a florisil short column to give (\pm)-**1b** (1.44 g, 84%). This acetate was dissolved in a mixed solvent of methanol (15 ml) and acetone (15 ml), then potassium carbonate (0.736 g, 1.1 equiv.) powder was added and the mixture was stirred for 12 h at rt. The resulting mixture was filtered through a florisil short column and evaporated to dryness. The resulting residue was dissolved in methanol (24 ml) and methyl iodide (2.55 g, 18 mmol) and potassium carbonate (1.38 g, 10 mmol) were added. The mixture was stirred for 5 days at rt, evaporated to dryness and purified by silica gel flash column chromatography to give (\pm)-[5-methoxy-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran-3-yl]methanol (**1e**) (1.07 g, 81%). Selected spectra data for (\pm)-**1e**: Bp 240°C, 1.6 Torr/Kugelrohr; *R*_f 0.6 (hexane/ethyl acetate = 1:1); IR (neat) 3364, 2835, 1614, 1514, 1487, 1250, 1176 cm⁻¹; ¹H NMR (270 MHz, CDCl₃, δ , ppm) 1.67 (1H, brs, OH), 3.44 (1H, dt, *J* = 8.7 Hz, 5.6 Hz), 3.68 (3H, s), 3.71 (3H, s), 3.80 (2H, dd, *J* = 8.6 Hz, 5.6 Hz), 5.43 (1H, d, *J* = 6.6 Hz), 6.60–6.71 (3H, m), 6.79 (2H, d, *J* = 8.96 Hz), 7.22 (2H, d, *J* = 8.2 Hz); ¹³C NMR (125 MHz, CDCl₃, δ) 30.72, 53.51, 55.09, 55.81, 64.02, 86.70, 109.29, 110.66, 113.63, 113.83, 127.04, 127.53, 127.70, 128.21, 133.66, 153.82, 154.03, 159.20 ppm. Anal calcd for C, 71.31; H, 6.34. Found for C, 71.55; H, 6.32.



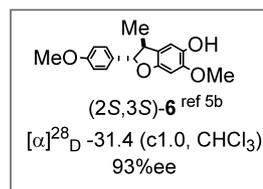
Scheme 2.

9. We initially tested lipase-catalyzed hydrolysis of acetate (\pm)-**1b**; however, the enantioselectivity was insufficient; the best enantioselectivity (E value¹⁰) was 11 for Novozyme 435 among tested nine enzymes. In addition, protection of the phenolic hydroxyl group of (\pm)-**1b** was unsuccessful and formed deacetylated (\pm)-**1a**. We therefore decided to investigate lipase-catalyzed transesterification of (\pm)-**1a**.
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12. Enantiomeric excess was determined as corresponding acetate by HPLC analysis (Diacel Chiralpak OD, hexane/*i*-PrOH = 8:1, 1.0 ml/min; R_t 8.6 min ((*2S,3S*)-**4e**), R_t 9.7 min ((*2R,3R*)-**4e**).
13. Preparation of **1e**, **1f**, and **1g** was accomplished as shown in Scheme 2.
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17. Absolute configuration of benzofuran ($-$)-**4e** (60% ee) was tentatively assigned to be (*2S,3S*) by indication of the sign of specific rotation of **5e** compared with the reported specific rotation value of (*2S,3S*)-2-methyl-3-(4-methoxy)phenyl-6-methoxy-2,3-dihydro-5-benzofuranol (**6**)^{5b} (Eq. (3-1)). Absolute configuration of benzofuran (+)-**1e** (87% ee) was assigned to be (*2R,3R*) by the same manner (Eq. (3-2)).



- ^a MeOH, K₂CO₃ (>90%)
^b MsCl, py, CH₂Cl₂ (>88%)
^c LiAlH₄, Et₂O (67~92%).



18. Another explanation may be possible: the poor enantioselectivity is due to the intramolecular or intermolecular acyl transfer reaction and protection of the hydroxyl group makes impossible such acyl transfer reaction between 2-hydroxymethyl group and 5-hydroxyl group in the reaction course.