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Asymmetric synthesis of (*R*)-(+)-6-(1,4-dimethoxy-3-methyl-2-naphthyl)-6-(4-hydroxyphenyl)hexanoic acid as a key intermediate for a neurodegenerative disease agent

Tomomi Ikemoto, Toshiaki Nagata,* Mitsuhisa Yamano, Tatsuya Ito, Yukio Mizuno and Kiminori Tomimatsu

Chemical Development Laboratories, Takeda Chemical Industries, Ltd., 2-17–85 Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan

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Abstract—An asymmetric synthesis of (*R*)-(+)-6-(1,4-dimethoxy-3-methyl-2-naphthyl)-6-(4-hydroxyphenyl)hexanoic acid **2** as a key intermediate for a neurodegenerative disease agent **1** has been developed. A key reaction was an asymmetric hydrogenation of hindered acrylic acid **13** catalyzed by the Rh-JOSIPHOS system in the presence of a base to afford a chiral acid up to 93% ee.

In a search for new therapeutic drugs for neurodegenerative diseases, a naphthoquinone derivative **1** was found to be a pharmaceutical agent useful for neurodegenetion inhibition in the prevention and treatment of nerve disease (Fig. 1).[1] Hence, the preparation of **1** on a large scale was required to support toxicological evaluation. For the synthesis of **1**, the key intermediate was optically active acid (*R*)-**2**. This was prepared by the enantioselective hydrolysis of the ester of *rac*-**2** using lipase on a large scale.[2] We continued to research a more efficient method, and found an asymmetric synthesis of (*R*)-**2**.

We planned the synthesis of (*R*)-**2** using asymmetric hydrogenation as shown in Scheme 1. While asymmetric hydrogenation has been extensively developed to produce chiral pharmaceuticals,[3] there were a few reports on the access of 1,1-bisaryl ethane derivatives.[4] In particular, the reduction of 1-naphthyl-1-aryl-ethene derivative as a hindered substrate has not been reported. In this letter, we report an asymmetric preparation of (*R*)-**2** using a new type of asymmetric reduction of hindered 1-naphthyl-1-aryl-ethene derivatives and the determination of its absolute configuration, which was not mentioned in the previous report.[2]

Initially, the model substrates were synthesized from naphthalene derivative **8**[2] in three steps, as shown in Scheme 2. Aldehyde **8** was converted by Horner–Wadsworth–Emmons reaction to *E*-α, β-unsaturated ester **9**.

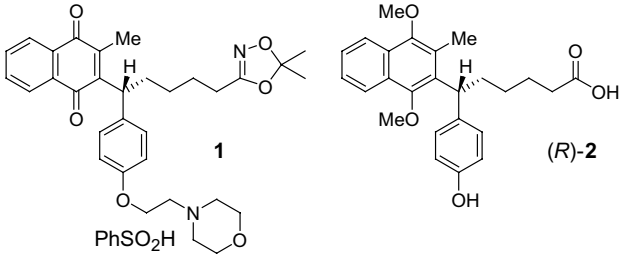
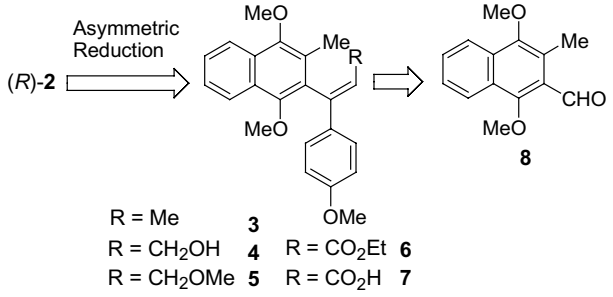


Figure 1.



Scheme 1.

Keywords: Asymmetric reduction; Rh-JOSIPHOS catalyst.
* Corresponding author. Tel.: +81 6 300 6378; fax: +81 6 300 6251; e-mail: nagata_toshiaki@takeda.co.jp

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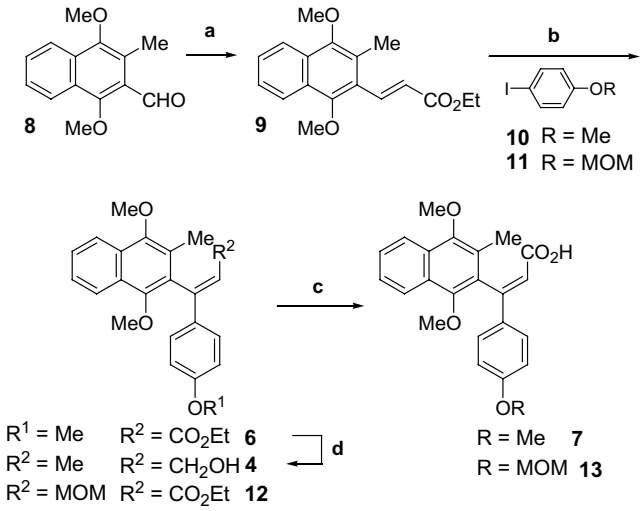


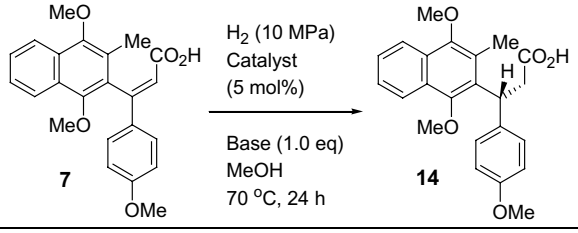
Scheme 2. Reagents and conditions; (a) $(EtO)_2P(O)CH_2CO_2Et$, *t*-BuONa, THF, 0–50 °C, 1 h, 94%, (b) $Pd(OAc)_2$ (10 mol%), $NaHCO_3$ (4 equiv), *n*-Bu_4 NBr (1 equiv), DMF, 100 °C, 50 h, 56% (**6**) or 57% (**12**), (c) 6 N NaOH, EtOH, 60 °C, 4 h, 92% (**7**) or 95% (**13**), (d) DIBAL, THF, −40 °C to rt, 98%.

Then, the Heck reaction of **9** with iodide **10** regioselectively afforded *Z*-**6** in 56% yield.[5] Ester **6** was converted to allylic alcohol **4** by DIBAL reduction in 98%. Furthermore, ester **6** was hydrolyzed to acrylic acid **7** in 92% yields.

For the initial experiments, allylic alcohol **4** was chosen as a model substrate, since Lepoittevin and co-workers have reported that the hydrogenation of 3,3-bisaryl allylic alcohols in the presence of [Rh(nbd)(*SS*-bdpp)]ClO_4 gave the enantioselective products in high selectivity (80–94% ee).[4] Therefore, the palladium, ruthenium and rhodium catalysts were employed to hydrogenate of allylic alcohol **4** in methanol at 70 °C under the pressure of hydrogen (10 MPa). However, no hydrogenations of **4** under these conditions were observed to provide byproduct **3** and **5** in 5% and 34% yields, respectively.[6] Stable allylic cations have been obtained by these reactions.[7] Furthermore, we thought that the olefins were too rigid and perhaps sterically hindered because atropisomerism[7] was observed in these substrates.

Next, we applied acrylic acid **7**, which were atropisomers, as model substrates to an asymmetric hydrogenation catalyzed by 5 mol% [Rh(nbd)(*SS*-bdpp)]ClO_4. Subsequently, we were pleased to find the reduction product **14**, which was not atropisomer, with good enantioselectivities in the case of the presence of various bases[8] as shown in Table 1. We considered that, the rho-

Table 1. Asymmetric catalytic hydrogenation of compound **7**



Entry[a]	Rh-catalyst[b]	Base	**14**/**7**[e]	% ee[e]
1	[Rh(nbd)(*SS*-bdpp)]ClO_4[f]	Et_3N[g]	90/10	85 (*R*)
2	[Rh(nbd)(*SS*-bdpp)]ClO_4[f]	Et_3N	93/7	86 (*R*)
3	[Rh(nbd)(*SS*-bdpp)]ClO_4[f]	KOH	96/4	86 (*R*)
4	[Rh(nbd)(*SS*-bdpp)]ClO_4[f]	(*S*)-MBA[h]	90/10	86 (*R*)
5	[Rh(nbd)(*SS*-bdpp)]ClO_4[f]	(*R*)-MBA[h]	89/11	86 (*R*)
6	[Rh(nbd)(*SS*-bdpp)]ClO_4[f]	Brucine	73/27	87 (*R*)
7	**A**[c,d] (*SS*)-BDPP[d]	Et_3N	97/3	87 (*R*)
8	**B**[c,d] (*R*)-BINAP[d]	Et_3N	18/41	6 (*R*)
9	**A**[c,d] (*SS*)-CHIRAPHOS[d]	Et_3N	15/68	27 (*R*)
10	**A**[c,d] (*SS*)-BCPM[d]	Et_3N	100/0	48 (*R*)
11	**A**[c,d] (*SS*)-BPPM[d]	Et_3N	85/15	45 (*R*)
12	**A**[c,d] (*RS*)-BPPFA[d]	Et_3N	100/0	3 (*S*)
13	**A**[c,d] (*RS*)-BPPFOH[d]	Et_3N	94/6	2 (*R*)
14	**A**[c,d] CARBOPHOS[d]	Et_3N	12/88	60 (*R*)
15	**C**[c,d] (*RR*)-Me-DuPHOS[d]	Et_3N	31/69	1 (*S*)
16	**C**[c,d] (*RR*)-Et-DuPHOS[d]	Et_3N	53/47	16 (*R*)
17	**A**[c,d] (*SR*)-JOSIPHOS[d]	Et_3N	95/5	94 (*R*)

[a] Standard conditions: 0.37 mmol of substance/catalysts 100/5.
[b] Abbreviations were used: nbd: norbordiene; cod: 1,5-cyclooctadiene.
[c] Rh catalyst; **A**: $[Rh(nbd)_2]ClO_4$, **B**: $[Rh(cod)_2]ClO_4$, **C**: $[Rh(nbd)_2]OTf$.
[d] These catalysts were prepared in situ by mixing $[Rh(dienes)_2]$(anions) (0.019 mmol) and chiral phosphines (0.019 mmol).
[e] Optical purity and conversion of **14** was confirmed by HPLC analyses.
[f] [Rh(nbd)(*SS*-bdpp)]ClO_4 catalyst was synthesized with $[Rh(nbd)_2]ClO_4$ and (*SS*)-BDPP in MeOH for 30 min and concentrated in vacuo.
[g] Et_3N (0.15 equiv) was used (entry 1).
[h] Optically active α-methylbenzylamine (MBA) was used as the base.

dium catalyst could strongly interact with the carboxyl group of substrate **7**, that the coordination was enhanced by these bases (entries 1–3), without undesirable elimination of the coordination group such as sterically hindered alcohol **4**, respectively. In particular, triethylamine played three important roles in this reduction. First, the solubility of **7** to methanol was extremely increased. Second, the chelating effect was enhanced against sterically hindered substrate. Third, the addition of triethylamine (1.0 equiv) slightly increased selectivity and conversion. Although, in addition, we would expect asymmetric kinetic resolution in the hydrogenation of **7**[9] with chiral bases, no inductions were observed (Table 1, entries 4–6).

Initially, a synthesized [Rh(nbd)(*SS*-bdpp)]ClO_4 catalyst was used (Table 1, entries 1–6). After researching, this process was more simplified to the use of an 'in-situ' catalyst system comprised of a 1:1 molar mixture of $Rh(dienes)_2ClO_4$ or $Rh(nbd)_2$ OTf and chiral phosphines (Table 1, entries 7–17). Though, the problems of catalyst oxygen stability were avoided by substituting two components of long-term stability.

Therefore, we explored a variety of chiral phosphines[10] more easily (Fig. 3; Table 1, entries 8–17) . The hydrogenation of **7** with Rh-CHIRAPHOS, Rh-DuPHOS or Rh-BINAP[11] catalysts showed lower enantioselectivities. In these events, unsaturated acid **7** could be asymmetrically hydrogenated with the Rh-JOSIPHOS[12] catalyst to afford (*R*)-**14**[13] of 94% ee in a high yield (entry 17).

Next, we tried an asymmetric hydrogenation of **13** (Scheme 3). Required **13** was prepared in the same manner as shown in Scheme 2. Then, acrylic acid **13** was hydrogenated with a catalyst, formed in situ from (*SR*)-JOSIPHOS and $[Rh(nbd)_2]ClO_4$, to afford **15**[14] of 93% ee[15] in a high yield as an oil. Therefore, chiral acid **15** was resolved to give (*R*)-isomer over 99% ee using its

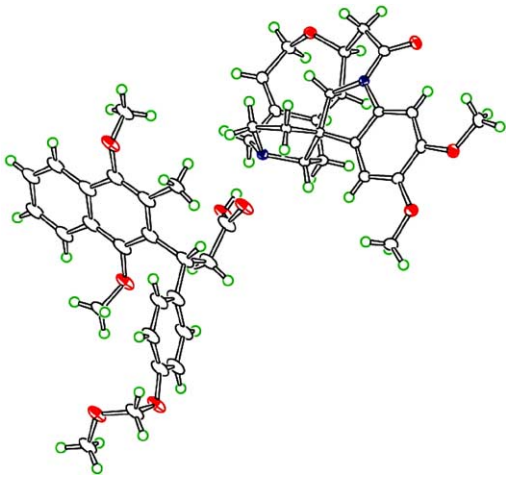


Figure 2. ORTEP view of **16**.

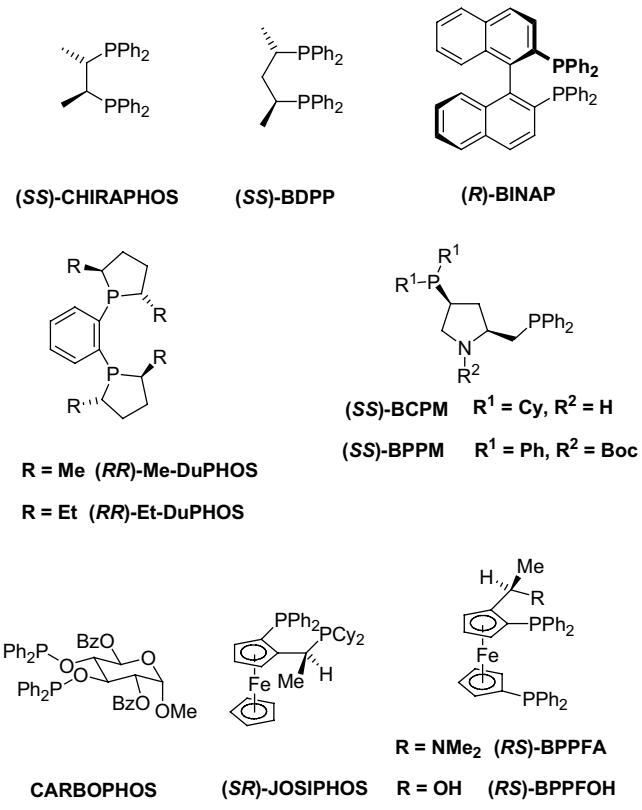
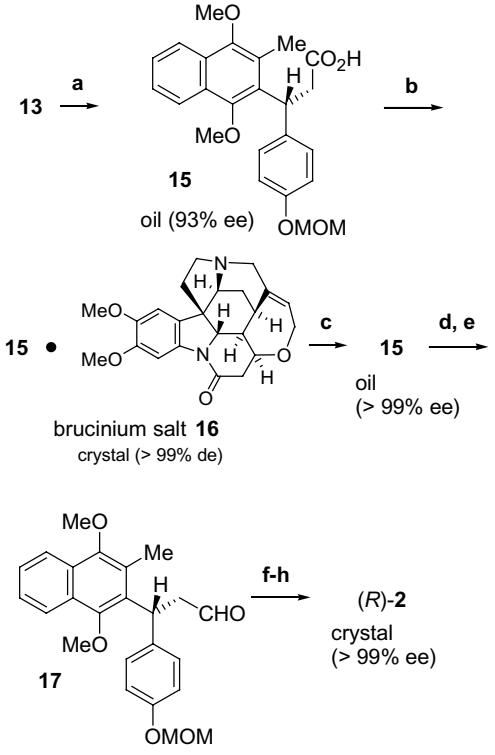


Figure 3. Chiral phosphines.



Scheme 3. Reagents and conditions; (a) H_2 (10 MPa), $[Rh(nbd)_2]ClO_4$ (5 mol%), (*SR*)-JOSIPHOS (5 mol%), Et_3N, MeOH, 70 °C, 63 h, conversion 94%, 93% ee, (b) brucine, acetone, rt, 86% (two steps), 99% de, (c) 1 N HCl, EtOAc, 95%, (d) (1) $ClCO_2Et$, Et_3N, (2) MeONHMe·HCl, DBU, MeCN, 88%, (e) Red-Al®, THF, 90%, (f) $Ph_3P(Cl)CH_2CH_2CO_2H$, $LiN(TMS)_2$, THF/DMSO (4/1), 56%, (g) H_2, 5% Pd–C, EtOH, 98%, (h) 6 N HCl, acetone, 75%.

brucinium salt **16**, which was easily purified by single crystallization in acetone, in 86% yield (two steps). Therefore, the absolute stereochemistry was determined by X-ray crystallography of **16** as shown in Figure 2.[16]

Salt **16** was acidified and extracted with EtOAc to give **15** in 99% ee. Condensation of **15** with *N*,*O*-dimethylhydroxylamine gave Weinreb amide, which was converted to aldehyde **17** by Red-Al® in 79% (two steps). The Wittig reaction[17] of aldehyde **17** followed by hydrogenation gave MOM ether of (*R*)-**2** in 43% yield (two steps). Finally, the MOM group was deprotected with 6 N HCl to give (*R*)-(+)-**2**[2] in 75% yield with >99% optical purity by a single recrystallization.

In conclusion, we have achieved the asymmetric synthesis of (*R*)-**2** by asymmetric reductions of **13** with the Rh-JOSIPHOS catalyst system in both high yield and enantioselectivity. Therefore, we could determine the absolute chemistry of (*R*)-**2** using brucinium salt **16**.

Acknowledgements

We thank Mr. Akio Kamimura for his help in the high-pressure laboratory. X-ray crystallographic analyses were performed by Ms. Keiko Higashikawa at the Medicinal Chemistry Research Laboratories. We also thank Mr. Tadao Kawarasaki, Mr. Syunsuke Shima and Mr. Tadashi Urai for their technical assistance.

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9. It was observed that the conversion rate of atropisomer **7** (t_R 10.3 min) was slightly faster than that of **7** (t_R 10.8 min). Therefore, the difference was not so affective to the enantiomeric excess as expected.
10. Chiral phosphines are shown in Figure 3.
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13. **14**. ^{1}H NMR (300 MHz, $CDCl_3$). δ 2.30 (br s, 3H), 3.06 (dd, $J = 16.23$, 6.39 Hz, 1H), 3.37–3.45 (dd, $J = 16.27$, 8.37 Hz, 1H), 3.42 (s, 3H), 3.64 (s, 3H), 3.76 (s, 3H), 5.15 (br m, 1H), 6.72 (dd, $J = 8.41$, 1.95 Hz, 2H), 7.03 (d, $J = 8.40$ Hz, 2H), 7.34–7.42 (m, 2H), 7.89–7.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 38.3, 55.6, 61.7, 62.4, 114.1, 122.7, 123.1, 125.8, 126.3, 127.0, 128.3, 128.6, 133.4, 135.4, 150.9, 151.1, 158.2, 178.6; IR (KBr) 1706 cm^{-1}; $[\alpha]_D^{20} + 81.53$ (*c* 0.536, MeOH); LRMS (EI, M^+) 380. Purity of **14** was confirmed by HPLC analysis (column: YMC-ODS A302 column, 4.6 i.d. × 150 mm, YMC; eluent: 0.05 M KH_2PO_4 aqueous solution/MeCN 55:45; flow rate: 1.0 mL/min; temperature: 25 °C; detector: 243 or 237 nm). Peaks of **7** and **14** were detected at t_R 20.5 and 21.4 min. Optical purity of **14** was confirmed by HPLC analysis using a chiral column (column: Chiralcel OJR column, 4.6 i.d. × 250 mm, Daicel Chemical Ind., Ltd; eluent: 0.5 M $NaClO_4$/0.5 M $HClO_4$/MeCN 100:1:101; flow rate: 0.5 mL/min; temperature: 25 °C; detector: 254 nm). Peaks of atropisomer **7** (two peaks), (*R*)-**14** and (*S*)-**14** were detected at t_R 10.3, 10.8, 12.0 and 16.8 min.
14. **15**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (br s, 3H), 3.13 (dd, $J = 15.30$, 6.34 Hz, 1H), 3.44 (s, 3H), 3.47 (dd, $J = 15.30$, 6.13 Hz, 1H), 3.51 (br s, 1H), 3.83 (s, 3H), 5.12 (s, 2H), 5.22 (br m, 1H), 6.92 (d, $J = 8.50$ Hz, 2H), 7.11 (d, $J = 8.50$ Hz, 2H), 7.43–7.49 (m, 2H), 7.97 (dd, $J = 6.40$, 2.96 Hz, 1H), 8.05 (dd, $J = 6.40$, 2.05 Hz, 1H); IR (KBr) 1706 cm^{-1}; $[\alpha]_D^{20} + 64.9$ (*c* 1.254, EtOAc). Purity of **15** was confirmed by HPLC analysis [column: YMC-ODS A302 column, 4.6 i.d. × 150 mm, YMC; eluent: 0.05 M KH_2PO_4 aqueous solution/MeCN 55:45; flow rate: 1.0 mL/min; temperature: 25 °C; detector: 243 or 237 nm] and peaks of **13** and **15** were detected at t_R 20.6 and t_R 21.2 min.
15. Optical purity of **15** was determined by hydrolyzing the MOM ether to the phenol with 6 N HCl and analyzing the phenol by HPLC using a Chiralcel OJR column [eluent: 0.5 M $NaClO_4$/0.5 M $HClO_4$/MeCN 100:1:101; flow rate: 0.5 mL/min; temperature: 25 °C; detector: 254 nm]. Peaks of acrylic acids (two peaks) and reduction products (two peaks) were detected at t_R 5.2, 5.6, 7.2 [(*R*)-isomer] and 10.3 [(*S*)-isomer] min.
16. While the IR, ^{1}H and ^{13}C NMR spectral data were in agreement with the proposed structure for brucinium salt **16**, confirmation of **15** was sorted by X-ray crystallography. CCDC 242134 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; tel: +44-0-1223-336408; fax: +44-0-1223-336033; or e-mail: linstead@ccdc.cam.ac.uk).
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