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TETRAHEDRON: *ASYMMETRY*

# Preparative resolution of a key intermediate for the synthesis of optically active *m*-phenylene $PGI_2$ derivatives

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**Abstract**

A key intermediate for the synthesis of optically active *m*-phenylene $PGI_2$ derivatives was efficiently resolved on a preparative scale by diastereomeric salt formation method using (+)-*cis*-*N*-benzyl-2-(hydroxymethyl)cyclohexylamine ((+)-*cis*-amine) as a resolving agent. 

## 1. Introduction

$PGI_2$, one of the natural prostaglandins, has been focused on since its discovery due to biological activities such as inhibition of platelet aggregation or vascular vasodilation. However, it readily decomposes in acidic or even neutral media because of the instability of its enol–ether linkage at C5–C6–O. We have developed a new $PGI_2$ analogue **1** with a *m*-phenylene skeleton at C5–C6–C7 in order to stabilize the enol–ether part in natural $PGI_2$ (Scheme 1).[1–5] We have also developed the stable analogue named Beraprost, whose sodium salt, Beraprost sodium, is now commercially available as an anti-platelet drug. With regard to the synthesis of Beraprost, which is a mixture of diastereomers, synthetic methods to racemic *m*-phenylene $PGI_2$ have been mainly described so far.[5] Synthetic methods to obtain optically active Beraprost are scarcely described.[3] In this report we will disclose the results of a study on the resolution, especially on a preparative scale, of a key intermediate carboxylic acid **4** for the synthesis of optically active *m*-phenylene $PGI_2$ derivative **5** (Scheme 2).

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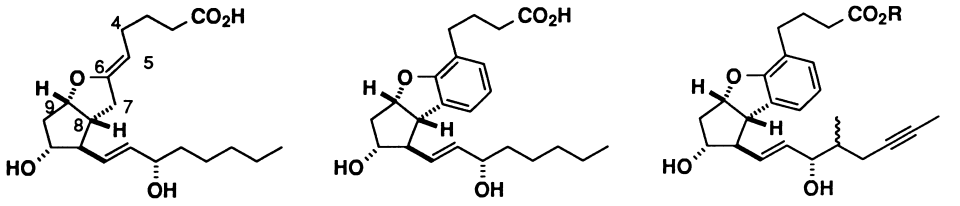
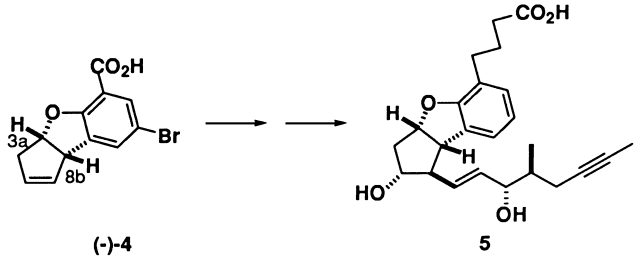



Scheme 1. $PGI_2$ and its derivatives




Scheme 2. Key intermediate **4** for the synthesis of optically active *m*-phenylene $PGI_2$ derivatives

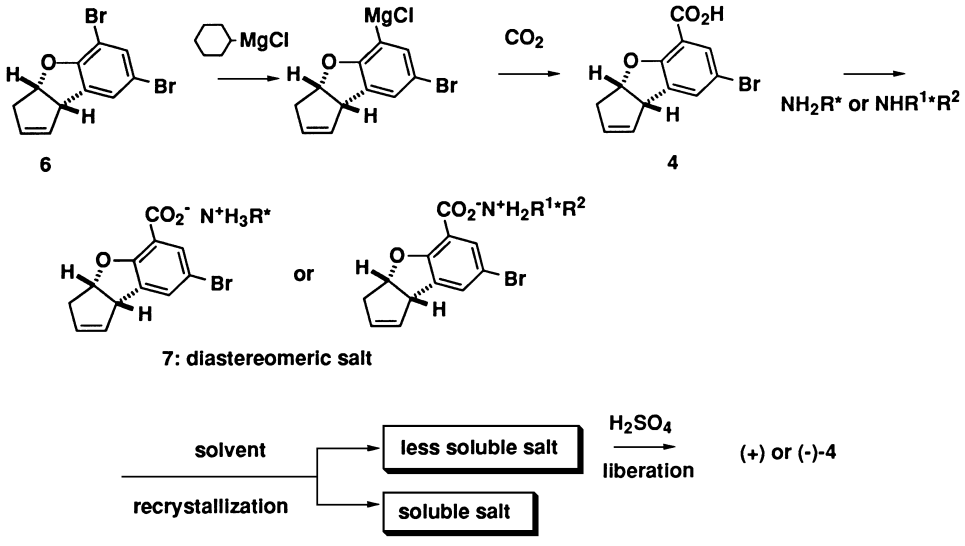
## 2. Results and discussion

We chose the carboxylic acid **4** as a suitable candidate towards synthesis of chiral Beraprost **5** for resolution using chiral amines because the corresponding carboxyl group on **4** is closely located to the asymmetric center C-3a. The racemic carboxylic acid **4** was prepared from the cyclopenta[*b*]benzofuran derivative **6** by regioselective Grignard exchange reaction[6] followed by carboxylation (Scheme 3). Treatment of **4** with various chiral amines **8**–**13** as resolving agents gave the corresponding diastereomeric salts **7** (Fig. 1). Table 1 shows the results of recrystallization of the diastereomeric salts on a small scale. Based on the resolution yields and the enantiomeric excesses, the resolving efficiency was calculated by their multiplication. Both the values of (−)-cinchonidine **8** and brucine **9** were low. On the other hand, two recrystallizations using commercially available (+)-*cis*-*N*-benzyl-2-(hydroxymethyl)cyclohexylamine ((+)-*cis*-amine) **11**[7] gave highly enantiomerically pure (−)-**4** in moderate yield (76%). Thus (+)-*cis*-amine **11** proved to be the most efficient reagent for the resolution of **4**. Next, resolution on a preparative scale for racemic **4** (100 g) was carried out by three recrystallizations from aqueous methanol with (+)-*cis*-amine **11** (77.9 g) to give enantiomerically pure (−)-**4** (31.1 g). From the mother liquid of the first recrystallization, (+)-**4** (45 g, 84.2% ee) was recovered and was again recrystallized twice with (−)-*cis*-amine to give enantiomerically pure (+)-**4** (19.1 g). Synthesis of enantiomerically pure Beraprost has already been reported by us using (−)-**4**.[3]

The absolute configuration of resolved (−)-**4** was determined by X-ray analysis of the methyl ester of (−)-**4** obtained by $CH_2N_2$ treatment. Fig. 2 shows a perspective view of the structure of the methyl ester of (−)-**4** which reveals that the configuration at both C-3a and C-8b is *S*.

## 3. Conclusion

In summary, the resolution of carboxylic acid **4** was efficiently achieved by the diastereomeric salt formation method using (+)-*cis*-amine **11** as the resolving agent, and highly enantiomerically pure (−)-**4** was obtained as the key intermediate of enantiomerically pure Beraprost.




Scheme 3. Preparation and resolution of the carboxylic acid **4**

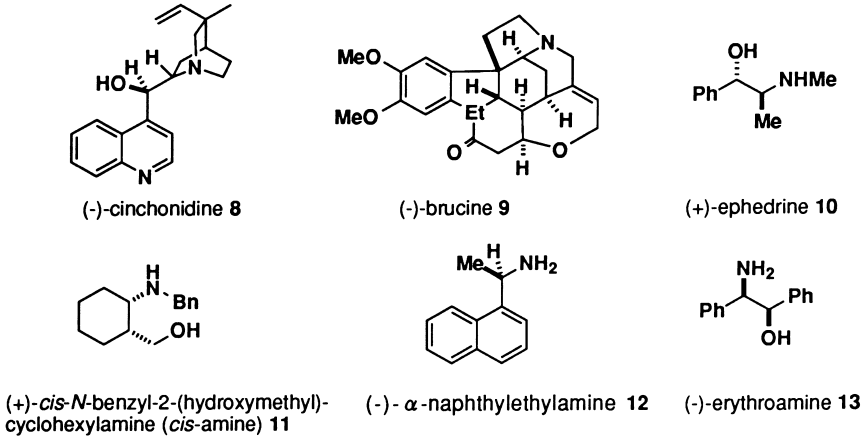



Figure 1. Optically active amines used for resolution of the carboxylic acid **4**

## 4. Experimental

### *4.1. General*

$^1$H NMR spectra of $CDCl_3$ solution were recorded with a Jeol GX270 spectrometer at 270 MHz. Infrared spectra were recorded with a Jasco A-3 spectrometer. MS spectra were recorded with a Hitachi RML 7-M or a Jeol JMS D-300 spectrometer. Melting points were determined on a Yanaco MP-500D melting point apparatus and are uncorrected. Analytical TLC was performed with Merck precoated (0.25 mm) silica gel plates. Specific rotations were measured with a Jasco DIP-140 polarimeter. Optical rotations were recorded at 20°C.

Table 1
Results of recrystallization of diastereomeric salts formed from the carboxylic acid **4** and a variety of chiral amines[a]

| chiral amine | solvent | number of recryst. times | yield (%) [b] | optical purity (%) [c] | sign on $[\alpha]_D$ of **4** | resolving efficiency [d] |
|---|---|---|---|---|---|---|
| (-)-cinchonidine **8** | MeOH/$H_2O$ =2/1 | 2 | 49 | 99 | - | 49 |
| brucine **9** | MeOH | 3 | 42 | 97 | + | 41 |
| (+)-ephedrine **10** | $CH_3CN$ | 1 | 90 | 82 | + | 74 |
| (+)-*cis*-*N*-benzyl-2-(hydroxymethyl)-cyclohexylamine (*cis*-amine) **11** | MeOH/$H_2O$ =1/1 | 2 | 76 | 100 | - | 76 |
| (-)-$\alpha$-naphthylethylamine **12** | MeOH/$H_2O$ =2/1 | 1 | 70 | 90 | - | 63 |
| (-)-erythroamine **13** | MeOH/$H_2O$ =2/1 | 2 | 68 | 98 | - | 67 |

a) This study was carried out by using 1-2 g of **4**. b) The yield was based on the 50% amount of carboxylic acid (**4**). c) Optical purity was calculated from the specific rotation of the optically pure sample. d) Yield (%) × optical purity (%)

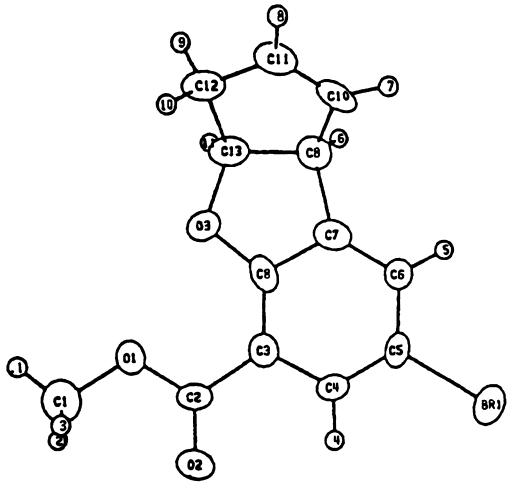



Figure 2. X-Ray structure of (−)-**4**. Selected bond distances (Å) and angles (°): Br(1)–C(5): 1.913(9); C(7)–C(9): 1.500(13); C(9)–C(10): 1.507(15); C(9)–C(13): 1.531(14); C(12)–C(13): 1.528(13); O(3)–C(13): 1.454(12); C(7)–C(9)–C(10): 114.7(8); C(7)–C(9)–C(13): 103.7(8); C(10)–C(9)–C(13): 104.8(8); C(9)–C(13)–C(12): 105.4(8); O(3)–C(13)–C(9): 106.3(7); O(3)–C(13)–C(12): 109.7(8)

### *4.2. (±)-3a,8b-*cis*-Dihydro-3*H*-5-carboxy-7-bromocyclopenta[*b*]benzofuran (±)-4*

To the solution of 3a,8b-*cis*-dihydro-3*H*-5,7-dibromocyclopenta[*b*]benzofuran **6** (711 g, 2.25 mol) in THF (1.5 L) was added 2.25 M cyclohexylmagnesium chloride (1.1 L, 2.48 mol) below 40°C. The solution was stirred at 30–40°C for 10 h. After the solution was cooled to below −20°C, $CO_2$ was bubbled through at the rate of ca. 1 L/min for 4 h. The mixture was poured into a mixture of ice (500 g) and 6N HCl (500 mL, 3 mol), and cyclohexane (1 L) was added to the resulting mixture. The precipitate was filtered and washed with EtOAc (2 L) and 2N HCl (2 L). The organic layer in the filtrate was separated

and concentrated to recover **4**. The combined **4** was washed with $H_2O$ (2 L×4) and EtOAc (2 L×3) and dried under reduced pressure to give pure **4** (499.3 g, 1.78 mol, 79%): mp 205–206°C; $^1$H NMR δ 2.83–3.01 (2H, m), 4.34–4.46 (1H, m), 5.59–5.68 (1H, m), 5.68–5.74 (1H, m), 5.77–5.87 (1H, m), 7.45 (1H, dd, *J*=2.0, 1.0 Hz), 7.81 (1H, d, *J*=2.4 Hz); IR (neat) 3200–2500, 1690, 1460, 1430, 1290, 1210, 1200, 1180, 950 cm$^{-1}$; LRMS m/e 282 ($M^+$ for $C_{12}H_9O_3{}^{81}Br$), 280 ($M^+$ for $C_{12}H_9O_3{}^{79}Br$); HRMS (EI) calcd for $C_{12}H_9O_3{}^{81}Br$: 281.9715, $C_{12}H_9O_3{}^{79}Br$: 279.9735. Found: 281.9730, 279.9755.

### 4.3. Resolution on a small scale

A mixture of **4** (1–2 g) and chiral amine (1 equiv.) was dissolved in a mixture of MeOH and $H_2O$ or MeOH or $CH_3CN$ by heating. The solution was cooled to rt and inoculated with a crystal of the salt having high optical purity. The solution was allowed to stand at rt for 1 day. The precipitate was filtered and dried. A part of the salt was treated with a mixture of EtOAc and 1N HCl. The organic layer was separated, washed with $H_2O$, and dried. The mixture was filtered and the obtained filtrate was evaporated to give crystals. The crystals were dried under reduced pressure and the $[\alpha]_D$ was measured.

### 4.4. (−)-3a,8b-cis-Dihydro-3H-5-carboxy-7-bromocyclopenta[b]benzofuran (−)-4

To the solution of **4** (100 g, 0.356 mol) and (+)-*cis*-*N*-benzyl-2-(hydroxymethyl)cyclohexylamine **11** (77.9 g, 0.355 mol) in MeOH (2 L) was added warm water (2 L, 50–60°C) under reflux. The solution was cooled to rt overnight. The precipitate was filtered and dried under reduced pressure to give the salt (85.9 g, 48% yield). The enantiomeric excess of (−)-**4** in the first crop was 88.4%, which was measured by a chiral HPLC column.

The first crop was dissolved in MeOH (1.8 L) by heating, and warm water (1.8 L, 50–60°C) was added to the solution. The solution was cooled to rt. The second crop was filtered and dried under reduced pressure to give the salt (64.8 g, 75% yield). The enantiomeric excess of (−)-**4** in the second crop was 98.6%. The same procedure was repeated by using the second crop (64.8 g, 0.129 mol), MeOH (1.3 L), and warm water (1.3 L) to give the third crop (51.5 g, 0.103 mol, 80% yield). The enantiomeric excess of (−)-**4** in the third crop was >99.0%.

The third crop (55.4 g, 0.111 mol) was treated with diluted $H_2SO_4$, and recrystallization from EtOAc gave (−)-**4** (31.1 g, 0.111 mol, 31% yield): mp 210.0–211.0°C; $^1$H NMR δ 2.74–3.00 (2H, m), 4.43 (1H, d, *J*=7.3 Hz), 5.60 (1H, t, *J*=6.1 Hz), 5.70–5.78 (1H, m), 5.78–5.85 (1H, m), 7.51 (1H, dd, *J*=2.4, 1.0 Hz), 7.72 (1H, d, *J*=2.0 Hz); IR (neat) 3450, 3000, 1690, 1440, 1265, 1205, 1160, 820 cm$^{-1}$; LRMS m/e 282 ($M^+$ for $C_{12}H_9O_3{}^{81}Br$), 280 ($M^+$ for $C_{12}H_9O_3{}^{79}Br$); HRMS (EI) calcd for $C_{12}H_9O_3{}^{81}Br$: 281.9715, $C_{12}H_9O_3{}^{79}Br$: 279.9735. Found: 281.9729, 279.9750; $[\alpha]_D$=−188.0 (c 0.5, EtOH).

### 4.5. Method for determination of the enantiomer excess of 4

A part (1–20 mg) of **4** or diastereomeric salt was suspended in $CH_3CN$ and treated with *p*-nitrophenacylbromide and diisopropylamine to give *p*-nitrophenacyl ester of **4**. The ester was analyzed by use of chiral HPLC column (sumipack OA-1000 (4 mm I.D.×25 cm), *n*-hexane:$CH_2Cl_2$:EtOH=88:11:1, detection at 285 nm). The peaks of (+)- and (−)-**4** were detected at the retention times of 30.5 min and 27.2 min, respectively.

### 4.6. (+)-3a,8b-cis-Dihydro-3H-5-carboxy-7-bromocyclopenta[b]benzofuran (+)-4

The mother liquid of the first crop described above was treated with diluted $H_2SO_4$, and recrystallization from EtOAc gave **4** containing (+)-isomer more (45 g, enantiomeric excess of (+)-**4** was 84.2%).

To the solution of thus obtained (+)-**4** (45 g, 0.160 mol) and (−)-*cis*-*N*-benzyl-2-(hydroxymethyl)cyclohexylamine (35.1 g, 0.160 mol) in MeOH (1.7 L) was added warm water (1.7 L, 50–60°C) under reflux. The solution was cooled to rt. The precipitate was filtered and dried under reduced pressure to give the salt (60.7 g, 76% yield). The enantiomeric excess of (+)-**4** in the first crop was 99.4%.

The diastereomeric salt was recrystallized twice from a mixture of MeOH and $H_2O$ to give the salt (37.0 g, 61% yield). The enantiomeric excess of (+)-**4** in the third crop was >99.5%.

The third crop (37.0 g, 73.9 mmol) was treated with diluted $H_2SO_4$ and recrystallization from EtOAc gave (+)-**4** (19.1 g, 67.9 mmol, 42% yield): mp 211.0–212.0°C; $^1$H NMR δ 2.74–3.00 (2H, m), 4.43 (1H, d, *J*=7.9 Hz), 5.61 (1H, t, *J*=6.1 Hz), 5.68–5.77 (1H, m), 5.77–5.83 (1H, m), 7.51 (1H, d, *J*=3.1 Hz), 7.72 (1H, d, *J*=2.4 Hz); IR (neat) 3450, 3000, 1690, 1440, 1265, 1205, 1160, 820 cm$^{-1}$; LRMS m/e 282 ($M^+$ for $C_{12}H_9O_3{}^{81}Br$), 280 ($M^+$ for $C_{12}H_9O_3{}^{79}Br$); HRMS (EI) calcd for $C_{12}H_9O_3{}^{81}Br$: 281.9715, $C_{12}H_9O_3{}^{79}Br$: 279.9735. Found: 281.9714, 279.9728; $[\alpha]_D$=+187.60 (c 0.5, EtOH).

### 4.7. Crystallography

The diffraction was measured at room temperature on an Enraf–Nonius CAD4 diffractometer using graphite-monochromated Mo-Kα radiation (λ=0.71073 Å) with an ω–θ scan method. The data were corrected for Lorenz polarization and absorption effects. The data were monitored by measuring three standard reflections every 41 min of X-ray exposure time. The structure was solved by heavy-atom method and Fourier methods and refined by full-matrix least squares. Non-hydrogen atoms were refined with anisotropic temperature factors using atomic scattering factors from the *International Tables for X-ray Crystallography*.[8] Hydrogen atoms were partially located from a difference density map and the rest were fixed at calculated positions.

### 4.8. Crystal data for methyl ester of (−)-4

The compound crystallized as needles. A crystal of the dimensions 0.25×0.15×0.1 mm was used for X-ray study; it belonged to the triclinic space group *P1*. Accurate cell dimensions and crystal orientation matrix were *a*=4.283(1) Å, *b*=10.970(2) Å, and *c*=13.593(3) Å, α=70.23(1)°, β=82.94(1)°, γ=80.32(1)°, *V*=591.0(1) Å$^3$, *D*=1.66 g/cm$^3$ for *Z*=2, *F*(000)=296 and absorption coefficient μ=36.8 cm$^{-1}$. A total of 2807 independent reflections were collected, 1318 observed for *I* greater than 3σ($I_0$). The final discrepancy factors were *R*=0.038 and w*R*=0.043. Refinement of the other enantiomer yielded significantly higher discrepancy indices (*R*=0.044, w*R*=0.050). All results reported herein refer to the enantiomer which yielded the lower *R*-values.

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## References


1. Ohno, K.; Nagase, H.; Matsumoto, K.; Nishiyama, H.; Nishio, S. In *Advances in Prostaglandin, Thromboxane, and Leukotriene Research;* Hayashi, O.; Yamamoto, S., Eds.; Ravan Press: New York, 1985; Vol. 15, pp. 279–281.
2. Ohno, K.; Nishiyama, H.; Nagase, H.; Matsumoto, K.; Ishikawa, M. *Tetrahedron Lett.* **1990**, *31*, 4489–4492.
3. Nagase, H.; Matsumoto, K.; Yoshiwara, H.; Tajima, A; Ohno, K. *Tetrahedron Lett*. **1990**, *31*, 4493–4494.
4. Nagase, H.; Matsumoto, K.; Nishiyama, H. *J. Synth. Org. Chem. Jpn.* **1996**, *54*, 1055–1066.
5. Wakita, H.; Matsumoto, K.; Yoshiwara, H.; Hosono, Y.; Hayashi, R.; Nishiyama, H.; Nagase, H. *Tetrahedron* **1999**, *55*, 2449–2474.
6. Nishiyama, H.; Isaka, K.; Itoh, K.; Nagase, H.; Matsumoto, K.; Yoshiwara, H. *J. Org. Chem.* **1992**, *57*, 407–410.
7. Nishikawa, J.; Ishizaki, T.; Nakayama, F.; Kawa, H.; Saigo, K.; Nohira, H. *Nippon Kagaku Kaishi* **1979**, 754–757.
8. *International Tables for X-ray Crystallography;* Kynoch Press: Birmingham, 1974; Vol. IV, Table 2.2B, 2.3.1.