Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2981–2989

TETRAHEDRON: *ASYMMETRY*

Preparative resolution of 2-methyl-4-hexynic acid for the synthesis of optically active *m*-phenylene PGI_2 derivatives and determination of their absolute configuration

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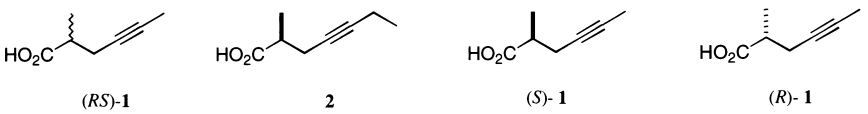
Received 29 May 2000; accepted 21 June 2000

Abstract

Racemic 2-methyl-4-hexynic acid, which is a starting material for the ω-side chain of the PGI_2 derivatives, Beraprost and Iloprost, was efficiently resolved on a preparative scale by diastereomeric salt formation using quinine and cinchonidine as resolving agents. Their absolute configuration was determined by X-ray analyses of Beraprost derivatives.

1. Introduction

2-Methyl-4-alkynic acids **1** and **2** are important as starting materials for the ω-side chain in the PGI_2 derivatives, Beraprost, Iloprost, and Cicaprost (Figs. 1 and 2).[1–3] In particular, Beraprost has been developed as an anti-platelet drug by us and consists of a mixture of four isomers, which are (8*S*,9*S*,16*S*)-form, (8*S*,9*S*,16*R*)-form, (8*R*,9*R*,16*R*)-form, and (8*R*,9*R*,16*S*)-form (Fig. 3).[4–7] In order to synthesize each isomer, it is necessary to obtain the corresponding enantiomers (*S*)-**1** and (*R*)-**1** of 2-methyl-4-hexynic acid (Fig. 1).



(*RS*)-**1** **2** (*S*)- **1** (*R*)- **1**

Figure 1. 2-Methyl-4-alkynic acid

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PII: S0957-4166(00)00251-2

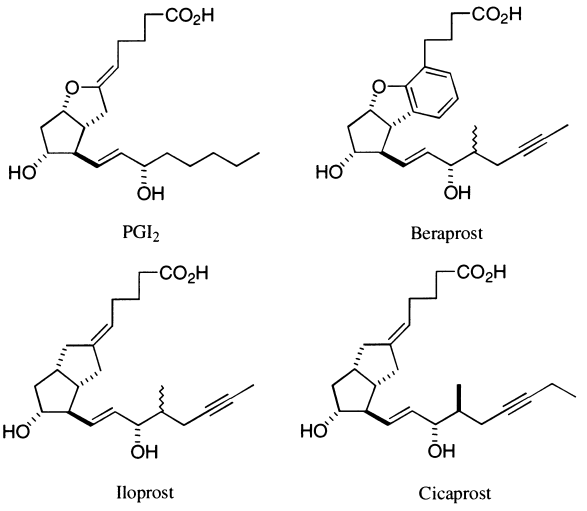


Figure 2. PGI_2 and its derivatives

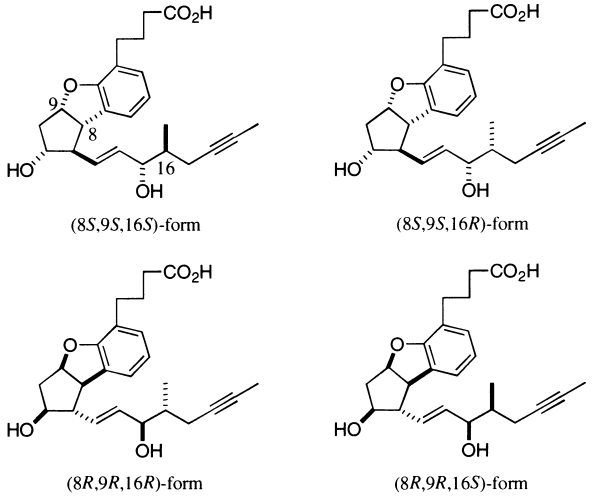


Figure 3. Four isomers constituting Beraprost

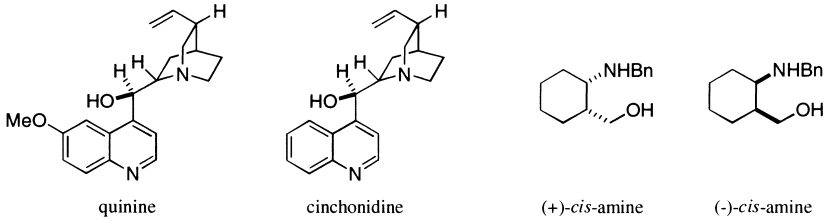
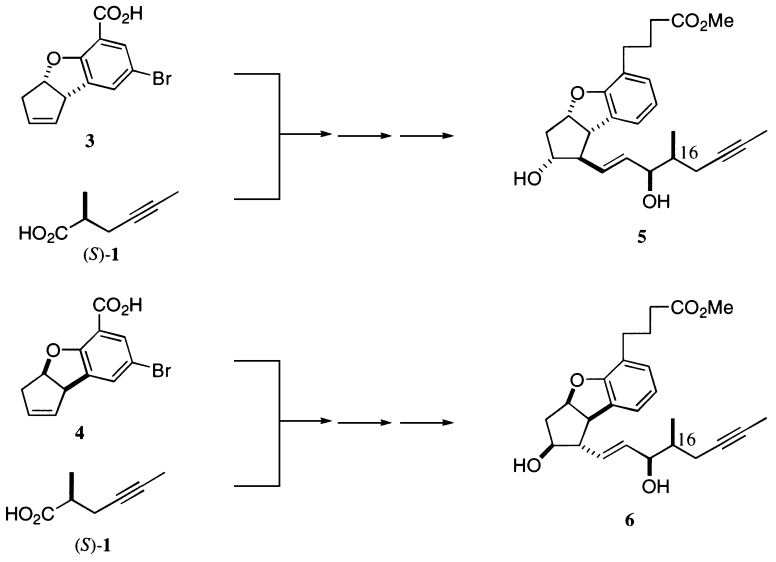


Figure 4. Optically active amines used for resolution of the carboxylic acid (*RS*)-**1**

Table 1
Results of recrystallization of diastereomeric salts formed from 2-methyl-4-hexynic acid (*RS*)-**1** and a variety of homochiral amines[a]

chiral amine	solvent	amount of solvent (volume/weight)	yield[b] (%)	e.e.[c] (%)	sign of specific rotation
quinine	$MeOH/H_2O$	6	52.0	45.1	-
cinchonidine	$MeOH/H_2O$	6	27.9	63.9	+
(+)-*cis*-amine	MeOH	2	18.4	20.8	-
(-)-*cis*-amine	MeOH	2	29.8	13.6	+

a) This study was carried out by using 1 g of 2-methyl-4-hexynic acid (*RS*)-**1**. b) The yield was based on the 50% amount of (*RS*)-**1**. c) e.e. was measured by conversion of the acid into its amide of (*S*)-(-)-α-methylbenzylamine and successive HPLC analysis.

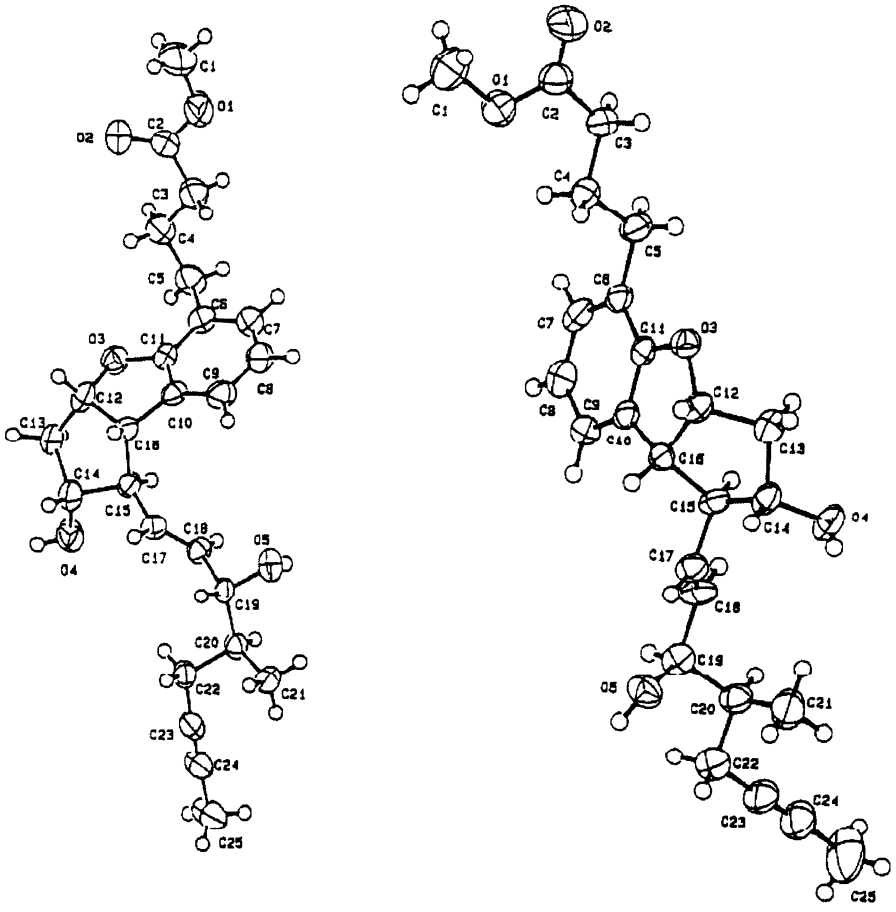


Scheme 1. The synthesis, from (–)-2-methyl-4-hexynic acid (*S*)-**1**, of Beraprost derivatives **5** and **6**

There are a few reports using asymmetric synthesis or commercially available homochiral starting materials for the synthesis of the enantiomer **2** of 2-methyl-4-heptynic acid.[8–10] However, there is no report for optically active 2-methyl-4-hexynic acid.[11] We have studied the synthesis of homochiral 2-methyl-4-hexynic acid (*S*)-**1** and (*R*)-**1** in order to synthesize optically active Beraprost and have succeeded in obtaining its enantiomers on a preparative scale. We disclose here the results of the study of its resolution and absolute configuration.

2. Results and discussion

We tried to resolve (*RS*)-**1** using seven chiral amines, that is to say, (+)-*cis*-*N*-benzyl-2-(hydroxymethyl)cyclohexylamine ((+)-*cis*-amine), (–)-*cis*-amine, quinine, cinchonine, strychnine, brucine, and cinchonidine, in various solvents (MeOH, EtOH, MeOH/H_2O, EtOH/H_2O, EtOAc, acetone, acetone–H_2O) on a small scale (Fig. 4). Among these chiral amines, only *cis*-amine, quinine and cinchonidine gave crystalline salts. The results of recrystallization of the diastereomeric salts are summarized in Table 1. The resolution yields and the enantiomeric excesses of *cis*-amine were low. On the other hand, recrystallization using commercially available quinine and cinchonidine gave moderately high enantiomeric excesses for (–)-2-methyl-4-hexynic acid (*S*)-**1** and (+)-2-methyl-4-hexynic acid (*R*)-**1**, respectively. Then these resolutions on a



5 **6**

Figure 5. X-Ray structure of Beraprost derivatives **5** and **6**. Selected bond distances (Å) and angles (°). Compound **5**: C(19)–O(5): 1.432(6); C(19)–C(20): 1.540(6); C(20)–C(21): 1.528(7); C(20)–C(22): 1.522(6); C(19)–C(20)–C(21): 111.6(4); C(19)–C(20)–C(22): 110.7(4); C(21)–C(20)–C(22): 110.2(4). Compound **6**: C(19)–O(5): 1.439(7); C(19)–C(20): 1.526(8); C(20)–C(21): 1.521(8); C(20)–C(22): 1.548(7); C(19)–C(20)–C(21): 111.1(6); C(19)–C(20)–C(22): 109.1(5); C(21)–C(20)–C(22): 110.7(5)

preparative scale for (*RS*)-**1** were carried out recrystallizing 10 times in aqueous methanol with quinine to give enantiomerically pure (*S*)-**1** (99.9% e.e.). From the mother liquid of the first and the second recrystallizations, (*R*)-**1** (49.0% e. e.) was recovered and again recrystallized nine times with cinchonidine to give enantiomerically pure (*R*)-**1** (99.6% e.e.).

The absolute configuration of resolved (*S*)-**1** was determined by X-ray analysis of Beraprost derivative **5**, which is the epimer at C-15 of the (8*S*,9*S*,16*S*)-form in the four isomers constituting Beraprost, and **6**, which is the (8*R*,9*R*,16*S*)-form of the four isomers constituting Beraprost (Scheme 1).[13] The two Beraprost derivatives **5** and **6** were synthesized by using (–)-carboxycyclopenta[*b*]benzofuran **3** and (+)-carboxycyclopenta[*b*]benzofuran **4**,[12] respectively, as starting materials.

Fig. 5 shows a perspective view of the structure of the Beraprost derivatives **5** and **6**. Both the absolute configurations at C-16 proved to be *S*.

Figs. 6 and 7 show crystal structures of the Beraprost derivatives **5** and **6**. In both of the crystals of **5** and **6**, two kinds of hydrogen bonding are found. In the case of **5**, one was the intermolecular hydrogen bonding between the hydroxyl group at C-11 and the carbonyl group at C-1 in another molecule in the 2_1 screw position and observed on the *a*–*c* plane. The other hydrogen bonding in **5** is the intermolecular hydrogen bonding between the hydroxyl group at C-15 and the hydroxyl group at C-15 in another molecule in the 2_1 screw position and exits along the *b*-axis. In the case of **6**, one is the intermolecular hydrogen bonding between the hydroxyl

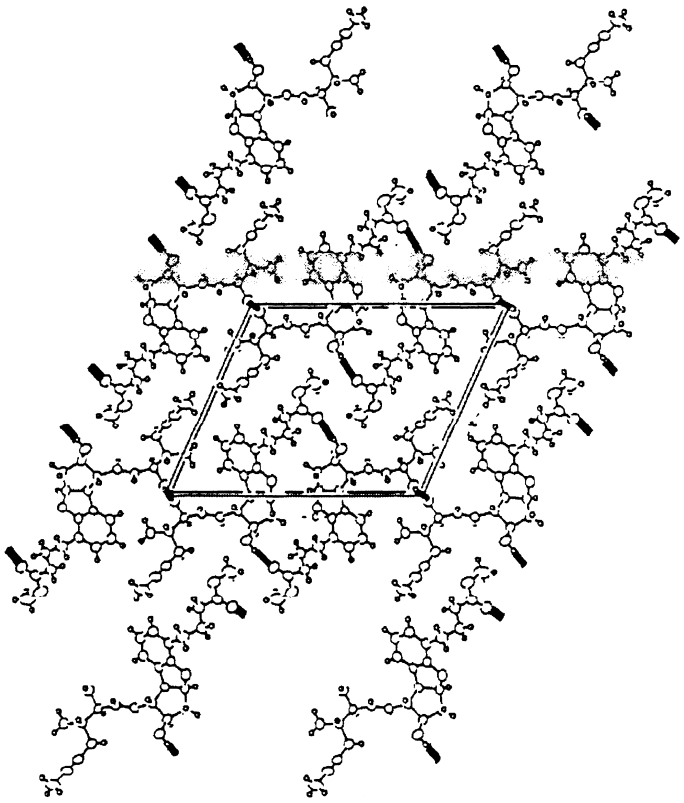


Figure 6. Crystal structure of **5**

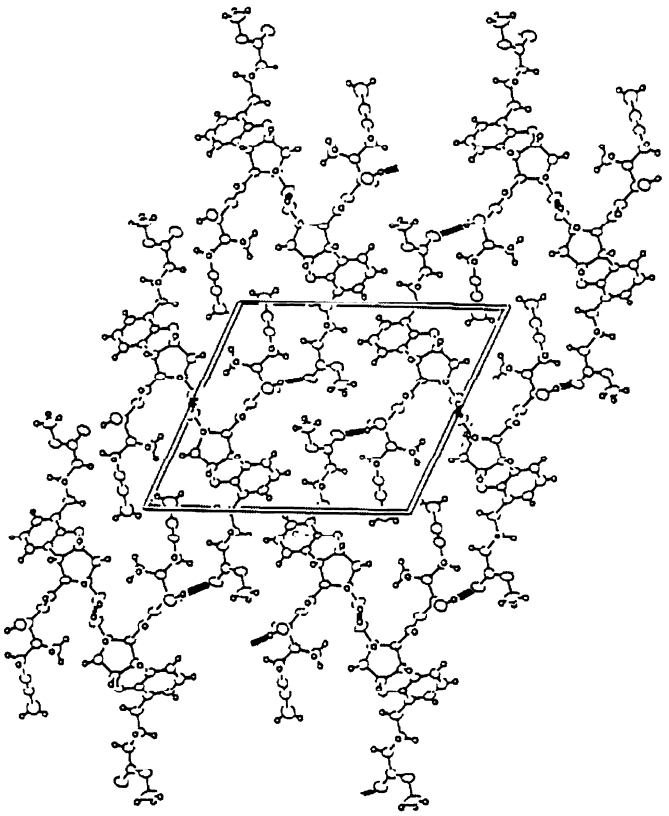


Figure 7. Crystal structure of **6**

group at C-11 and the hydroxyl group at C-11 in another molecule in the 2_1 screw position and observed along the *b*-axis. The other hydrogen bonding in **6** is the intermolecular hydrogen bonding between the hydroxyl group at C-15 and the carbonyl group at C-1 in another molecule in the translation position and exits on the *a*–*c* plane. These differences of the hydrogen bonding cause the difference between the conformation of the side chain of **5** and that of the side chain of **6**. For example, with regard to conformation of the α-side chain, positional relation of four atoms, that is to say, O1–C2–C3–C4, in **5** is *trans* (Fig. 5). On the other hand, positional relation of O1–C2–C3–C4 in **6** is almost eclipsed. With regard to conformation of the ω-side chain, positional relation of six atoms, that is to say, C17–C18–C19–C20–C22–C23, in **5** is *gauche*–*gauche*–*trans* (Fig. 5). On the other hand, the positional relation of C17–C18–C19–C20–C22–C23 in **6** is *gauche*–*trans*–*trans*.

3. Conclusion

The resolution of 2-methyl-4-hexynic acid (*S*)-**1** and (*R*)-**1** was efficiently achieved by diastereomeric salt formation using quinine and cinchonidine as resolving agents. Their absolute configurations were determined by X-ray analyses of Beraprost derivatives.

4. Experimental

4.1. General

^{1}H NMR spectra of $CDCl_3$ solution were recorded with a JEOL GX270 spectrometer at 270 MHz. IR spectra were recorded with a JASCO A-3 spectrophotometer. MS spectra were recorded with a Hitachi RML 7-M or JEOL JMS D-300 spectrometer. Specific rotations were measured with a JASCO DIP-140 polarimeter and recorded at 20°C.

4.2. Study of optical resolution on a small scale

A mixture of (*RS*)-**1**[2] (1.0 g) and chiral amine was dissolved in a mixture (1:1) of MeOH and H_2O or MeOH only. The solution was allowed to stand at –15°C. The precipitate was filtered and a part of the salt was acidified to give free carboxylic acid. The enantiomeric excess of the obtained acid was measured by the method described below. The results on this small scale are shown in Table 1.

4.3. Method for determination of the enantiomeric excess of (S)-*1* or (R)-*1*

A part (ca. 100 mg) of (*S*)-**1** or (*R*)-**1** was converted into acid chloride using thionyl chloride (ca. 100 μL) in toluene (2 mL). The acid chloride was added to a mixture of (*S*)-(–)-α-methylbenzylamine (ca. 250 mg), Et_3N (280 μL), and THF (2.5 mL) at 0°C in order to convert the acid into its amide. The reaction mixture was monitored by TLC (EtOAc:cyclohexane = 1:2, R_f value of the acid and the amide = 0.57 and 0.26, respectively). The reaction mixture was treated with H_2O and extracted with EtOAc. The organic layer was washed with 1N HCl and brine and dried over $MgSO_4$. The organic layer was filtered and evaporated. A part (ca. 20 mg) of the residue was dissolved in EtOH (1 mL) and analyzed by use of HPLC column (YMC A-014 (6 mm I.D. ×30 cm), *n*-hexane:CH_2Cl_2:EtOH = 88:10:2, detection at 254 nm, flow rate 0.8 mL/min, column temperature 40°C). The peaks of (*R*)-**1** and (*S*)-**1** were detected at retention times 32 and 40 min, respectively.

4.4. (–)-2-Methyl-4-hexynic acid (R)-*1*

(±)-2-Methyl-4-hexynic acid (*RS*)-**1** (155.6 g, 1.23 mol) and quinine (400 g, 1.23 mol) were dissolved in MeOH (500 g) under reflux. To the solution was added H_2O (500 g) and the solution was allowed to stand at –10 to +5°C. The precipitate was filtered and dried under reduced pressure to give the 1st crop (226.0 g, 81.4% yield). The e.e.s of the 1st crop and its mother liquid were (–)-67.6% and (+)-49.0%, respectively. The 1st crop (225 g, 0.500 mol) was dissolved in MeOH (225 g) under reflux. After the dissolution of the salt, H_2O (225 g) was added and the solution was cooled at 0°C. The precipitate was filtered and dried under reduced pressure to give 192 g (85.3% yield, (–)-88.1% e.e.).

The 2nd crop was recrystallized eight times from MeOH–H_2O to give diastereomer salt, 35.0 g (12.6% yield, (–)-99.9% e.e., $[\alpha]_D = -143.3$ (*c* 1.95, EtOH)).

The 10th crop (34 g) was acidified by using 2N sulfuric acid (200 mL) and the mixture was extracted with EtOAc (500 mL). The organic layer was washed with brine (500 mL). The organic layer was dried over $MgSO_4$ and evaporated. Distillation from the residue gave (–)-2-methyl-4-hexynic acid (*S*)-**1**

(9.1 g, 0.072 mol, 11.7% yield, 99.9% e.e.): bp 82.5–84.0°C/1.5–2 mmHg; ^{1}H NMR δ 1.28 (3H, d, J = 6.9 Hz), 1.78 (3H, t, J = 2.5 Hz), 2.25–2.43 (1H, m), 2.43–2.78 (2H, m); IR (neat) 3100–3000, 2978, 1707, 1701, 1464, 1418, 1292, 1243, 1208 cm^{-1}; $[\alpha]_D$ = –0.72 (*c* 10.0, EtOH); LRMS (EI) *m*/*e* 126 (M^+); HRMS calcd for $C_7H_{10}O_2$ 126.0681, found 126.0652.

4.5. (+)-2-Methyl-4-hexynic acid (R)-*1*

The (+)-2-methyl-4-hexynic acid (351.5 g, 2.79 mol, (+)-49.0% e.e., bp 115–118°C/9–10 mmHg), which was obtained by acidification of the mother liquid of the 1st and 2nd crops of (–)-2-methyl-4-hexynic acid, and cinchonidine (820 g, 2.79 mol) were dissolved in MeOH (1 kg) under reflux. To the solution was added H_2O (1.1 kg) and the solution was allowed to stand at 0–5°C for 5 days. The precipitate was filtered and dried under reduced pressure to give 532 g (1.27 mol, 45.4% yield, (+)-76.1% e.e.). The 1st crop (531 g, 1.27 mol) was dissolved in MeOH (800 g) under reflux. After the dissolution of the salt, H_2O (800 g) was added and the solution was allowed to stand at 0–5°C for 7 days. The precipitate was filtered and dried under reduced pressure to give 361 g (67.9% yield, (+)-89.3% e.e.).

The 2nd crop was recrystallized seven times from MeOH–H_2O to give diastereomer salt, 80.0 g (6.8% yield, (+)-99.6% e.e., $[\alpha]_D$ = –98.1 (*c* 2.15, EtOH)).

The 9th crop (79 g) was acidified by using 2N sulfuric acid (375 mL) and the mixture was extracted with EtOAc (500 mL). The organic layer was washed with brine (500 mL). The organic layer was dried over $MgSO_4$ and evaporated. Distillation from the residue gave (+)-2-methyl-4-hexynic acid (*R*)-**1** (21.9 g, 0.174 mol, 6.2% yield, 99.6% e.e.): bp 79.0–81.0°C/1.5 mmHg; ^{1}H NMR δ 1.28 (3H, dd, J = 6.9, 1.0 Hz), 1.78 (3H, t, J = 1.7 Hz), 2.25–2.42 (1H, m), 2.42–2.75 (2H, m); IR (neat) 3100–3000, 2978, 1707, 1465, 1420, 1293, 1244, 1208 cm^{-1}; $[\alpha]_D$ = +0.97(c 10.1, EtOH); LRMS (EI) *m*/*e* 126 (M^+); HRMS calcd for $C_7H_{10}O_2$ 126.0681, found 126.0679.

4.6. Crystallography

The diffraction was measured at room temperature on a Rigakudenki AFC-5R 4-circle diffractometer using graphite-monochromated Cu-Kα radiation (λ = 1.54178 Å) with an ω–2θ scan method. The data were corrected for Lorenz-polarization. No significant changes were observed in the intensities of three standard reflections measured periodically throughout the data collection. The structure was solved by direct method using SHELXS-86 and non-hydrogen atoms were refined by anisotropic temperature factors. The hydrogen atoms attached to the oxygen atoms were located from difference Fourier maps and refined by isotropic temperature factors. The remaining hydrogen atoms attached to the carbon atoms were located by calculation (C–H = 0.95 Å) and not refined. The structure was refined by full-matrix least squares. The absolute configuration of **5** and **6** was determined based on the configuration of the cyclopenta[*b*]benzofuran skeleton.[12,13]

4.7. Crystal data for *5*

The compound crystallized as needles. A crystal of dimensions 0.5×0.08×0.04 mm was used for X-ray study; it belonged to the monoclinic space group $P2_1$. Principal cell parameters were as follows: a = 15.044(2) Å, b = 4.8467(6) Å, c = 17.074(2) Å, β = 113.809(8)°, V = 1139.0(2) Å^3, D = 1.203 g/cm^3 for Z = 2, $F(000)$ = 444 and absorption coefficient μ = 6.3 cm^{-1}. Of the 2016

reflections which were collected, 1935 were unique and 1403 observed for I greater than $3\sigma(I_0)$ were used for the refinement. The final discrepancy factors were $R=0.037$ and $wR=0.038$.

4.8. Crystal data for **6**

The compound crystallized as needles. A crystal of dimensions $0.5\times0.1\times0.05$ mm was used for X-ray study; it belonged to the monoclinic space group $P2_1$. Principal cell parameters were as follows: $a=14.602(3)$ Å, $b=4.817(2)$ Å, and $c=17.515(3)$ Å, $\beta=113.74(1)^\circ$, $V=1127.7(4)$ Å^3, $D=1.215$ g/cm^3 for $Z=2$, $F(000)=444$ and absorption coefficient $\mu=6.3$ cm^{-1}. Of the 2011 reflections which were collected, 1928 were unique and 1025 observed for I greater than $3\sigma(I_0)$ were used for the refinement. The final discrepancy factors were $R=0.037$ and $wR=0.038$.

Acknowledgements

We gratefully acknowledge the late Dr. K. Ohno for his leadership and passion. We would like to thank Dr. T. Tajima, Ms. M. Kajita, Mr. Y. Hosono, and Mr. R. Hayashi for analytical support.

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