Bioscience, Biotechnology, and Biochemistry

ISSN: 0916-8451 (Print) 1347-6947 (Online) Journal homepage: https://www.tandfonline.com/loi/tbbb20

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To cite this article: Shunsuke Konishi, Yusuke Ogura, Hirosato Takikawa & Hidenori Watanabe (2019): Asymmetric synthesis of *trans-p*-menth-3-ene-1,2,8-triol, the monoterpene isolated from herbal plants, Bioscience, Biotechnology, and Biochemistry, DOI: 10.1080/09168451.2019.1671789

To link to this article: https://doi.org/10.1080/09168451.2019.1671789

BIOSCIENCE, BIOTECHNOLOGY, AND BIOCHEMISTRY
https://doi.org/10.1080/09168451.2019.1671789

Asymmetric synthesis of *trans-p*-menth-3-ene-1,2,8-triol, the monoterpene isolated from herbal plants

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ABSTRACT

The monoterpene, *trans-p*-menth-3-ene-1,2,8-triol, is a naturally occurring alcohol isolated from several herbal plants. In the present work, the asymmetric synthesis of both enantiomers of this natural product was achieved using Sharpless asymmetric dihydroxylation as the key step. A reversal of enantiofacial selectivity was observed in the asymmetric dihydroxylation.

ARTICLE HISTORY
Received 3 September 2019
Accepted 18 September 2019

KEYWORDS
Asymmetric synthesis; asymmetric dihydroxylation; monoterpene; absolute configuration

In 2010, Liu et al. reported the isolation of a novel monoterpene alcohol from the Chinese herb, *Mentha haplocalyx* [1]. However, the proposed structure in that study, 3,3,5-trimethyl-2-oxabicyclo[2.2.2]oct-5-en-4-ol (**1**), was proven to be incorrect by our group's synthetic studies [2]. During our synthetic studies, we also found that the ^{1}H and ^{13}C NMR data (in CD_3OD) reported for the monoterpene isolated from *Mentha haplocalyx* [1] were in good agreement with those reported for three other natural monoterpenes: asiasarinol (**2**), comosoxide B (**3**), and *cis-p*-menth-3-ene-1,2,8-triol (*cis*-**4**) (Figure 1). Asianarinol was isolated from the wild ginger *Asiasarum sieboldii* in 1999, and its structure was proposed as compound **2** [3]. Comosoxide B was isolated from the Thai herb *Curcuma comosa* in 2008, and **3** was proposed as its structure [4,5]. *cis-p*-Menth-3-ene-1,2,8-triol [(1*R**,2*S**)-4-(1′-hydroxy-1′-methylethyl)-1-methylcyclohex-3-ene-1,2-diol] (*cis*-**4**) was first isolated from the liverwort *Riella helicophylla* in 1999 [6], and then from the tropical American tree *Protium heptaphyllum* in 2002 [7] and *A. sieboldii* in 2012 [8]. These facts suggested that these four independently isolated natural products [1,3,4,7] would have an identical structure. We noted that the references [6] and [8] did not report the NMR data in CD_3OD. However, our synthetic studies on **2, 3**, and *cis*-**4** verified the incorrectness of the proposed structures that had appeared in the literatures [1,3,4,7]. On the basis of careful reconsideration of the NMR data, we proposed *trans-p*-menth-3-ene-1,2,8-triol [(1*R**,2*R**)-4-(1′-hydroxy-1′-methylethyl)-1-methylcyclohex-3-ene-1,2-diol] (*trans*-**4**) as the genuine structure of these natural monoterpenes, and the correctness of the *trans*-**4** structure was confirmed by our racemic synthesis [2]. Nevertheless, the absolute configuration of this natural product has remained unknown. In addition, the reported specific rotation values are considerably discrete as follows: $[\alpha]_D^{20}$ − 12.6 (*c* 0.005, MeOH) [1]; $[\alpha]_D^{27}$ + 18.1 (*c* 1.1, MeOH) [4]; $[\alpha]_D^{20}$ + 2 (*c* 0.2, MeOH) [7]. These unknown or ambiguous data prompted us to investigate the asymmetric synthesis of *trans*-**4**. In the present work, we describe the first asymmetric synthesis of *trans*-**4**.

Results and discussion

Sharpless asymmetric dihydroxylation (AD) with AD-mix reagents is recognized as one of the most powerful and reliable method for preparing optically active 1,2-diols [9–11]. As shown in Scheme 1, we envisaged adopting AD methodology to synthesize optically active *trans*-**4** via two different routes. In route A, the known diene **5** [12,13] was selected as the substrate for AD. Alternatively, alcohol **6** was selected as the substrate for route B.

Initially, the known diene **5** was exposed to AD-mix-α (route A in Scheme 1) under standard conditions to afford the corresponding diol **7** (A-α;prepared via route A with AD-mix-α) in 40% yield with 34% ee. Based on our previous racemic synthesis [2], the resulting **7** (A-α) was converted to the diastereomeric mixture of *cis*-/*trans*-**4** (A-α) (dr = 4:1) via three steps: treatment with MeLi, Dess-Martin oxidation, and Luche reduction. The yielded mixture of *cis*-/*trans*-**4** (A-α) was separated by SiO_2 column chromatography to give pure *trans*-**4** (A-α) in 47% yield (three steps). The enantiomeric purity of (+)-*trans*-**4** (A-α) could be enriched up to 99.5% ee (determined by chiral GLC analysis) by repeated recrystallization. We then carried out AD reaction of **5** with AD-mix-β. However, surprisingly, the enantiomeric

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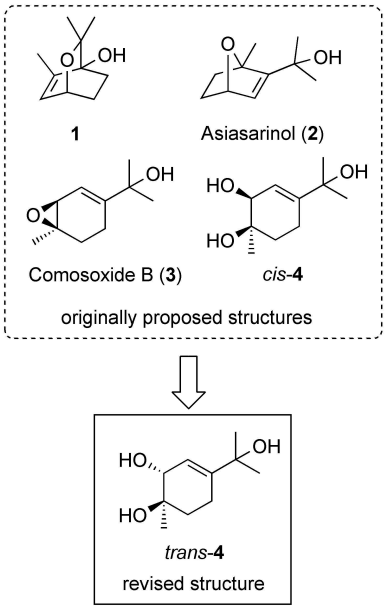
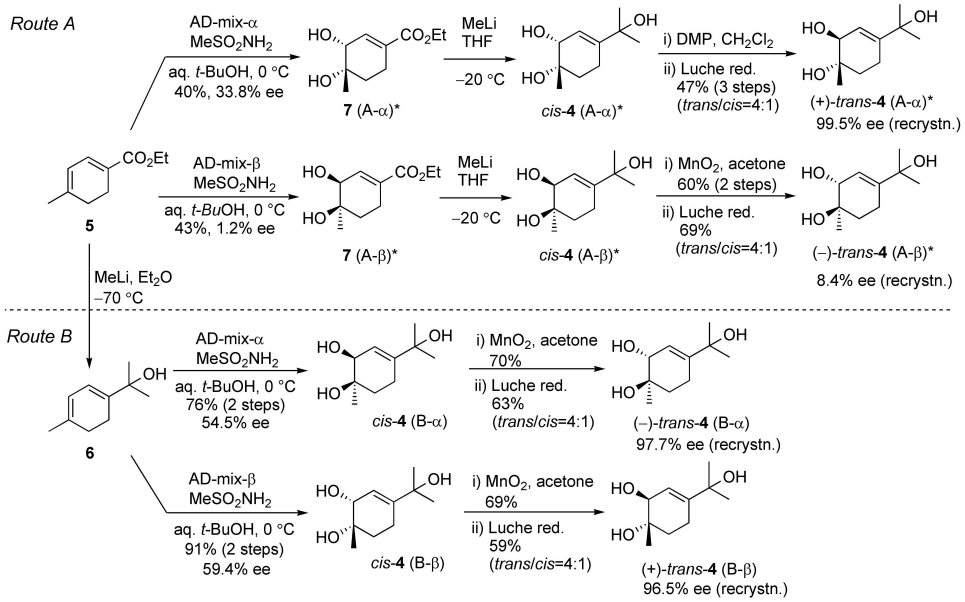


Figure 1. Structures of **1** and the related monoterpenes.

excess of the yielded **7** (A-β) was estimated to be only 1.2%. Although this low enantiomeric outcome was unexpected and disappointing, the unusual mismatch between the enantiomeric purities of **7** (A-α; 34% ee) and **7** (A-β; 1.2% ee) could be explained by the fact that the chiral ligands in AD-mix α/β reagents were not enantiomers but pseudo-enantiomers to each other. Meanwhile, we converted **7** (A-β) to *trans*-**4** (A-β) (42% in three steps). It should be noted that MnO_2 was adopted for the oxidation of *cis*-**4** (A-β) instead of Dess-Martin periodinane because of comparatively low cost and ease of experimental procedure. However, the enantiomeric purity of (−)-*trans*-**4** (A-β) was far from satisfactory (8.4% ee) even after recrystallizations. It should be noted that the absolute configurations of **7**, *cis*-**4**, and *trans*-**4** (A-α and A-β series) were discussed and confirmed later.

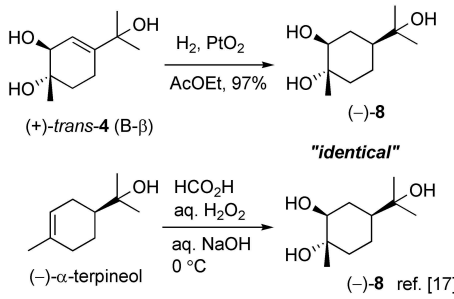
Following the above-mentioned unsatisfactory results, we then focused our attention on route B to prepare both enantiomers of *trans*-**4** with high enantiomeric purity. Substrate **6** was prepared from **5** by treatment with MeLi. Alcohol **6** was exposed to AD-mix-α and -β, affording *cis*-**4** (B-α) (76% in two steps, 55% ee) and *cis*-**4** (B-β) (91% in two steps, 59% ee), respectively. Although the observed enantioselectivities were not satisfactory, we continued the synthesis of both enantiomers of *trans*-**4** because we had already learned that the enantiomeric purity of *trans*-**4** could be enriched by recrystallization. Thus, in the same manner, we converted *cis*-**4** (B-α) and *cis*-**4** (B-β) into (−)-*trans*-**4** (B-α) (44% in two steps) and (+)-*trans*-**4** (B-β) (40% in two steps), respectively. The enantiomeric purities of (−)-*trans*-**4** and (+)-*trans*-**4** were successfully enriched up to 97.7% ee and 96.5% ee, respectively, via recrystallization.

Although the asymmetric synthesis of both enantiomers of *trans*-**4** was achieved, there was a dissonance of enantiofacial selectivity in AD reactions. In other words, (+)-*trans*-**4** was obtained with AD-mix-α in route A, and (−)-*trans*-**4** was obtained with the same AD-mix-α reagent in route B. According to the Sharpless AD face-selection rule, the same AD-mix reagent should yield the same enantiomer of *cis*-/*trans*-**4** via both routes. Therefore, an unexpected reversal of enantiofacial selectivity in AD was occurring in either route A or B. To our knowledge, there are a couple of papers reporting the reversal of facial selectivity of AD-mix on achiral trisubstituted alkenes [10,14–16]. In order to clarify the



* The absolute configurations of compounds with astarisk (*) are drawn based on the final conclusion.

Scheme 1. Synthesis of *trans*-**4**.



Scheme 2. Determination of the absolute configuration of *trans*-**4**.

absolute configuration of synthetic *trans*-**4**, we converted (+)-*trans*-**4** (B-β) into the known compound **8**. As shown in Scheme 2, hydrogenation of (+)-*trans*-**4** was successfully catalyzed by PtO_2 to give (−)-**8** as a single isomer (97%). On the basis of comparison of the specific rotation value and chiral GLC analysis, the synthetic (−)-**8** derived from (+)-*trans*-**4** (B-β) was confirmed to be identical to that from (−)-α-terpineol [17]. Thus, finally, we concluded that the unexpected reversal of enantiofacial selectivity of AD was expressed in route A (Scheme 1).

The specific rotations of the naturally occurring and synthetic *trans*-**4** are listed in Table 1. Based on the absolute value of the specific rotation, the enantiomeric purities of all of the naturally occurring *trans*-**4** are likely moderate to low.

Conclusion

In summary, we achieved the first synthesis of both enantiomers of *trans*-**4** using AD-mix reagents. Since an unexpected reversal of the enantiofacial selectivity in AD reaction was observed, the absolute configuration of synthetic *trans*-**4** was verified unambiguously by conversion of *trans*-**4** into the known compound **8**.

Experimental

General procedures

All air- and/or water-sensitive reactions were carried out under Ar atmosphere in dry solvents. Solvents were dried as follows: THF and Et_2O over sodium-benzophenone, CH_2Cl_2 over P_2O_5. All melting points (mps) were uncorrected. Melting points were recorded on a Yanaco Melting Point Apparatus. IR spectra were measured with a Jasco FT/IR-230 spectrophotometer. ^1H NMR (300, 400 or 500 MHz) and ^{13}C NMR (75, 100 or 125 MHz) data were recorded by JEOL JNM AL300, JEOL ECS400 or JEOL JNM LA500, respectively. Chemical shifts (δ) were referenced to the residual solvent peak as the internal standard ($CDCl_3$: $\delta_H = 7.26$, $\delta_C = 77.0$; C_6D_6: $\delta_H = 7.15$, $\delta_C = 128.4$; CD_3OD: $\delta_H = 3.30$, $\delta_C = 49.0$; acetone-d_6: $\delta_H = 2.04$, $\delta_C = 206.0$). Optical rotations were measured on a Jasco P-1030 polarimeter. Mass spectra were recorded on JEOL JMS SX102 or JEOL JMS-T100GCV. The enantiomeric excess was determined by gas chromatography using chiral separative column. The carrier gas was helium with a flow rate of 0.7 mL/min. Injector and detector temperatures were 230°C and 250°C, respectively. The oven temperature was 40–180°C, raised at 0.7°C/min. Column chromatography was performed on Merck silica gel 60 (0.060–0.200 mm), TLC was carried out on Merck glass plates pre-coated with silica gel 60 F_{254} (0.25 mm) and preparative TLC was carried out on Merck glass plates pre-coated with silica gel 60 F_{254} (0.5 mm).

Table 1. Specific rotation values of natural and synthetic *trans*-**4**.

Source	Specific rotation
Mentha haplocalyx [1]	$[\alpha]_D^{20}$ − 12.6 (*c* 0.005, MeOH)
Curcuma comosa [4]	$[\alpha]_D^{27}$ + 18.1 (*c* 1.1, MeOH)
Protium heptaphyllum [7]	$[\alpha]_D^{20}$ + 2 (*c* 0.2, MeOH)
Synthetic (−)-*trans*-**4**	$[\alpha]_D^{19}$ − 55 (*c* 0.50, MeOH)
Synthetic (+)-*trans*-**4**	$[\alpha]_D^{15}$ + 55 (*c* 0.50, MeOH)

Ethyl (3R,4S)-3,4-dihydroxy-4-methylcyclohex-1-en-1-carboxylate [(−)-7 (A-α)]

To a solution of **5** (1.54 g, 9.28 mmol) in *t*-BuOH (50 mL) and water (50 mL) were added $MeSO_2NH_2$ (1.44 g, 15.1 mmol) and AD-mix-α (15.6 g, 11.1 mmol) successively at 0°C. After stirring for 3 d at the same temperature, the reaction mixture was poured into sat. aq. $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane/EtOAc (1/1) gave (−)-**7** (A-α) (746 mg, 3.73 mmol, 40.1%) as a colorless solid with 33.8% ee. Chiral GLC analysis: 10%AcTBDMSBCD+40% PentylTBDMSBCD (30 m, ID 0.25 mm, film 0.25 μm), t_R = 187.0 min (minor) and t_R = 191.0 min (major); mp 68–71°C; $[\alpha]_D^{30}$ − 27.8 (*c* 0.50, MeOH); HR-FIMS *m*/*z* calcd for $C_{10}H_{16}O_4$ $[M]^+$ 200.1049, found 200.1054. IR, ^1H-NMR, and ^{13}C-NMR data were identical to those of the racemate [2].

(1S,2R)-4-(1′-hydroxy-1′-methylethyl)-1-methyl-cyclohex-3-ene-1,2-diol [(−)-cis-4 (A-α)]

To a solution of MeLi (1.14 M in Et_2O; 3.25 mL, 3.71 mmol) in THF (3 mL) was added a solution of (−)-**7** (A-α) (92.8 mg, 0.463 mmol) in THF (1.5 mL) at −20°C. After stirring for 20 min at the same temperature, the reaction mixture was poured into sat. aq. NH_4Cl and extracted with EtOAc. The organic layer was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue (68.3 mg) was directly used for the next step without purification. An analytical

sample was obtained by column chromatography on silica gel (CH_2Cl_2-MeOH, 10/1) as a white solid. mp 121–122°C; $[\alpha]_D^{25}$ – 18.1 (*c* 0.50, MeOH); HR-FIMS *m/z* calcd for $C_{10}H_{18}O_3$ $[M]^+$ 186.1256, found 186.1247. IR, ^{1}H-NMR, and ^{13}C-NMR data were identical to those of the racemate [2].

(1S,2S)-4-(1′-hydroxy-1′-methylethyl)-1-methylcyclohex-3-ene-1,2-diol [(+)-trans-4 (A-α)]

To a solution of crude (–)-*cis*-**4** (A-α) (33.7 mg, 0.181 mmol) in CH_2Cl_2 (5 mL) were added $NaHCO_3$ (excess amount) and DMP (307 mg, 0.724 mmol) at room temperature. After stirring for 2 d, the reaction mixture was poured into sat. aq. $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through silica gel, and the concentration of the filtrate afforded *the corresponding ketone (A-α)*, which was directly used for the next step without purification. An analytical sample was obtained by column chromatography on silica gel (CH_2Cl_2-MeOH, 20/1) as a yellow viscous oil. $[\alpha]_D^{29}$ – 27.0 (*c* 0.50, MeOH); HR-FIMS *m/z* calcd for $C_{10}H_{16}O_3$ $[M]^+$ 184.1099, found 184.1097. IR, ^{1}H-NMR, and ^{13}C-NMR data were identical to those of the racemate [2].

To a solution of *the above-mentioned ketone (A-a)* (31.4 mg) in MeOH (5 mL) was added $CeCl_3 \cdot 7H_2O$ (191 mg, 0.513 mmol) at –50°C. After stirring for 5 min, to the resulting mixture was added $NaBH_4$ (9.5 mg, 0.26 mmol) at the same temperature. After stirring for 20 min, the reaction mixture was diluted with CH_2Cl_2 and chromatographed over silica gel. Elution with CH_2Cl_2/MeOH (20/1 to 10/1) gave (+)-*trans*-**4** (A-α) (20.2 mg, 0.108 mmol, 47.0% in three steps) as a white solid. Note that a considerable amount of *cis*-**4** (A-α) was observed as a byproduct, but not isolated. The obtained (+)-*trans*-**4** (A-α) was recrystallized three times from EtOAc to give the enantiomerically enriched (+)-*trans*-**4** (A-α). The enantiomeric excess was determined by chiral GLC analysis to be 99.5% ee: 10%AcTBDMSBCD +40%PentylTBDMSBCD (30 m, ID 0.25 mm, film 0.25 μm), t_R = 190.6 min (major) and t_R = 190.9 min (minor). mp 106–107°C; $[\alpha]_D^{15}$ + 55.7 (*c* 0.50, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.15 (3H, s), 1.29 (6H, s), 1.61–1.72 (2H, m), 2.11 (1H, m), 2.23 (1H, dt, *J*= 17.6, 5.6 Hz), 3.92 (1H, m), 5.59 (1H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 21.85, 24.14, 29.00, 29.06, 34.70, 72.50, 72.89, 74.75, 122.29, 147.03. HR-FIMS *m/z* calcd for $C_{10}H_{18}O_3$ $[M]^+$ 186.1256, found 186.1252.

Ethyl (3S,4R)-3,4-dihydroxy-4-methylcyclohex-1-en-1-carboxylate [(+)-7 (A-β)]

In the same manner, as described for the preparation of (–)-**7** (A-α), **5** (8.64 g) was converted to 3.01 g (43.0%, 1.2% ee) of (+)-**7** (A-β) by using AD-mix-β instead of AD-mix-α. (+)-**7** (A-β): a colorless solid; mp 78°C; $[\alpha]_D^{27}$ + 0.33 (*c* 0.50, MeOH); HR-FIMS *m/z* calcd for $C_{10}H_{16}O_4$ $[M]^+$ 200.1049, found 200.1056. IR, ^{1}H-NMR, and ^{13}C-NMR data were identical to those of the racemate [2].

(1R,2S)-4-(1′-hydroxy-1′-methylethyl)-1-methylcyclohex-3-ene-1,2-diol [(+)-cis-4 (A-β)]

In the same manner as described for the preparation of (–)-*cis*-**4** (A-α), (+)-**6** (A-β) (1.42 g, 6.55 mmol) was converted to crude (+)-*cis*-**4** (A-β). An analytical sample was obtained by chromatography on silica gel as a colorless solid. mp 121–122°C; $[\alpha]_D^{26}$ + 0.97 (*c* 0.50, MeOH); HR-FIMS *m/z* calcd for $C_{10}H_{18}O_3$ $[M]^+$ 186.1256, found 186.1255. IR, ^{1}H-NMR, and ^{13}C-NMR data were identical to those of the racemate [2].

(1R,2R)-4-(1′-hydroxy-1′-methylethyl)-1-methylcyclohex-3-ene-1,2-diol [(–)-trans-4 (A-β)]

To a solution of crude (+)-*cis*-**4** (A-β) (6.55 mmol) in acetone (20 mL) was added MnO_2 (88%; 3.3 g, 33 mmol) at room temperature. After stirring for 2 d, the reaction mixture was filtered through a pad of Celite and chromatographed over silica gel. Elution with hexane/EtOAc (1/2) gave *the corresponding ketone (A-β)* (790 mg, 4.29 mmol, 60.4% in two steps) as a yellow viscous oil. $[\alpha]_D^{27}$ + 0.80 (*c* 0.50, MeOH); HR-FIMS *m/z* calcd for $C_{10}H_{16}O_3$ $[M]^+$ 184.1099, found 184.1090.

In the same manner, as described for the preparation of (+)-*trans*-**4** (A-α), *the above-mentioned ketone (A-β)* (31.4 mg, 0.171 mmol) was converted to (–)-*trans*-**4**–(A–β) (22.1 mg, 0.119 mmol, 69.4%) as a colorless solid. This was recrystallized from EtOAc to give the slightly enriched (–)-*trans*-**4**–(A–β) of 8.4% ee. mp 132–133°C; $[\alpha]_D^{25}$ – 1.64 (*c* 0.50, MeOH); HR-FIMS *m/z* calcd for $C_{10}H_{18}O_3$ $[M]^+$ 186.1256, found 186.1264. IR, ^{1}H-NMR, and ^{13}C-NMR data were identical to those of the racemate [2].

1-(1′-hydroxy-1′-methylethyl)-4-methylcyclohexa-1,3-diene (6)

To the solution of **5** (4.99 g, 30.0 mmol) in Et_2O (150 mL) was added MeLi (1.14 M in Et_2O, 66 mL, 75 mmol) at –70°C. After stirring for 30 min, the reaction mixture was poured into sat. aq. NH_4Cl and extracted with Et_2O. The organic layer was

washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue (4.57 g) was used directly in the next step without purification. An analytical sample was obtained by column chromatography on silica gel (pentane-Et_2O, 3/1) as a slightly yellow oil. IR (film): ν_{max} 3376, 3036, 2973, 2873, 1657, 1448, 1375, 1158, 952, 825 $cm^{-1;}$ ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (6H, s), 1.78 (3H, s), 2.09 (2H, t, *J*= 9.2 Hz), 2.22 (2H, t, *J*= 9.2 Hz), 5.66 (1H, d, *J*= 5.2 Hz), 5.85 (1H, d, *J*= 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.88, 23.32, 28.53, 29.09, 72.62, 116.39, 119.07, 135.06, 141.83; HR-FIMS *m/z* calcd for $C_{10}H_{16}O$ $[M]^+$ 152.1201, found 152.1205.

(1R,2S)-4-(1′-hydroxy-1′-methylethyl)-1-methyl-cyclohex-3-ene-1,2-diol [(+)-cis-4 (B-α)]

To a solution of the crude **6** (1.16 g, 7.64 mmol) in *t*-BuOH (40 mL) and water (40 mL) were added $MeSO_2NH_2$ (945 mg, 9.93 mmol) and AD-mix-α (10.7 g, 7.64 mmol) successively at 0°C. After stirring for 6 d at the same temperature, $MeSO_2NH_2$ (363 mg, 3.82 mmol) and AD-mix-α (5.35 g, 3.82 mmol) were added to the reaction mixture. After stirring for 2 d, the reaction mixture was poured into sat. aq. $Na_2S_2O_3$. After saturation of the aqueous layer with NaCl, this mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with CH_2Cl_2 /MeOH (50/1 to 10/1) gave (+)-*cis*-**4** (B-α) (1.076 g, 5.78 mmol, 75.6% in two steps) as a white solid. The enantiomeric purity was determined by chiral GLC analysis to be 54.5% ee: 10%AcTBDMSBCD+40%PentylTBDMSBCD (30 m, ID 0.25 mm, film 0.25 μm), t_R = 182.2 min (major) and t_R = 183.4 min (minor). mp 120–121°C; $[\alpha]_D^{18}$ + 28.9 (*c* 0.50, MeOH); HR-FIMS *m/z* calcd for $C_{10}H_{18}O_3$ $[M]^+$ 186.1256, found 186.1265. IR, ^1H-NMR, and ^{13}C-NMR data were identical to those of the racemate [2].

(1R,2R)-4-(1′-hydroxy-1′-methylethyl)-1-methyl-cyclohex-3-ene-1,2-diol [(−)-trans-4 (B-α)]

In the same manner as described for the preparation of (−)-*trans*-**4** (A-β), (+)-*cis*-**4** (B-α) (1.01 g, 5.43 mmol) was converted to *the corresponding ketone (B-α)* (700 mg, 3.80 mmol, 70.0%) as a slightly yellow viscous oil. $[\alpha]_D^{19}$ + 44.3 (*c* 0.50, MeOH); HR-FIMS *m/z* calcd for $C_{10}H_{16}O_3$ $[M]^+$ 184.1099, found 184.1105.

This ketone (368 mg, 2.00 mmol) was converted to (−)-*trans*-**4** (B-α) (234 mg, 1.26 mmol, 62.8%) as a colorless solid. Note that *cis*-**4** (B-α) was obtained as a byproduct (11.9%). The obtained (−)-*trans*-**4** (B-α) was recrystallized from EtOAc to give the enantiomerically enriched (−)-*trans*-**4** (B-α) of 97.7% ee. mp 107°C; $[\alpha]_D^{19}$ − 55.2 (*c* 0.50, MeOH); HR-FIMS *m/z* calcd for $C_{10}H_{18}O_3$ $[M]^+$ 186.1256, found 186.1263. IR, ^1H-NMR, and ^{13}C-NMR data were identical to those of the racemate [2].

(1S,2R)-4-(1′-hydroxy-1′-methylethyl)-1-methyl-cyclohex-3-ene-1,2-diol [(−)-cis-4 (B-β)]

In the same manner, as described for the preparation of (+)-*cis*-**4** (B-α), the crude **6** (1.83 g, 12.0 mmol) was converted to (−)-*cis*-**4** (B-β) (2.04 g, 10.9 mmol, 91.1%, 59.4% ee) as a colorless solid. mp 120°C; $[\alpha]_D^{16}$ − 28.9 (*c* 0.50, MeOH); HR-FIMS *m/z* calcd for $C_{10}H_{18}O_3$ $[M]^+$ 186.1256, found 186.1262. IR, ^1H-NMR, and ^{13}C-NMR data were identical to those of the racemate [2].

(1S,2S)-4-(1′-hydroxy-1′-methylethyl)-1-methyl-cyclohex-3-ene-1,2-diol [(+)-trans-4 (B-β)]

In the same manner as described for the preparation of (−)-*trans*-**4** (A-β), (−)-*cis*-**4** (B-β) (1.95 g, 10.5 mmol) was converted to *the corresponding ketone (B-β)* (1.33 g, 7.21 mmol, 68.7%) as a slightly yellow viscous oil. $[\alpha]_D^{20}$ − 49.8 (*c* 0.50, MeOH); HR-FIMS *m/z* calcd for $C_{10}H_{16}O_3$ $[M]^+$ 184.1099, found 184.1098.

This ketone (B-β) (664 mg, 3.60 mmol) was converted to (+)-*trans*-**4** (B-β) (395 mg, 2.12 mmol, 58.9%) as a colorless solid. This was recrystallized from EtOAc to give the enantiomerically enriched (+)-*trans*-**4** (B-β) of 96.5% ee. mp 105–106°C; $[\alpha]_D^{15}$ + 54.6 (*c* 0.50, MeOH); HR-FIMS *m/z* calcd for $C_{10}H_{18}O_3$ $[M]^+$ 186.1256, found 186.1261. IR, ^1H-NMR, and ^{13}C-NMR data were identical to those of the racemate [2].

(1S,2S,4S)-4-(1′-hydroxy-1′-methylethyl)-1-methyl-cyclohexane-1,2-diol [(−)-8]

To a solution of (+)-*trans*-**4** (B-β) (50 mg, 0.27 mmol, 96.5% ee) in EtOAc (10 mL) was added PtO_2 (5 mg). The mixture was stirred under H_2 (0.3 MPa) at room temperature. After the reaction was completed (5 h), the mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with CH_2Cl_2/MeOH (10/1) gave (−)-**8** (49 mg, 0.26 mmol, 97%, 97.8% ee†) as a white solid. mp 115.5–116°C; $[\alpha]_D^{20}$ − 3.2 (*c* 0.42, EtOH); IR ($CHCl_3$ soln.): ν_{max} 3609, 3012, 2978, 2945, 2871, 1467, 1371, 1069 $cm^{-1;}$ ^1H NMR (500 MHz, acetone-d_6) δ 1.08 (3H, s), 1.12 (6H, s), 1.10–1.19 (2H, m), 1.34–1.45 (2H, m), 1.65–1.71 (2H, m), 1.89 (1H, dddd, *J*= 2.5, 3.5, 4.5, 13.0 Hz), 3.17 (1H, s), 3.32 (1H, s), 3.42 (1H, ddd, *J*= 4.0, 4.5, 11.5 Hz), 3.50 (1H, s); ^{13}C NMR (125 MHz, acetone-d_6) δ 19.10, 24.86, 27.41, 27.48, 33.16, 39.14, 48.35, 71.23, 73.39, 77.78; HR-FIMS *m/z* calcd for $C_{10}H_{20}O_3$ $[M]^+$ 188.1412, found 188.1411. †) The ee of (−)-**8** was silghtly higher than that of the starting *trans*-**4** (B-β). Although the reason is not certain,

this might be caused by accuracy of peak separation/detection.

We also prepared (−)-**8** from (−)-α-terpineol according to the reported procedure [17].The identicalness of the absolute configurations of two synthetic (−)-**8** was confirmed by chiral GLC analysis: 40% AcTBDMSBCD+10%PentylTBDMSBCD (30 m, ID 0.25 mm, film 0.25 μm), t_R = 183.5 min (major) and t_R = 185.0 min (minor).

Acknowledgments

Our thanks are due to T. Hasegawa Co., Ltd. for financial support.

Author contribution

H.W. designed this study. S.K. carried out the experiments. H. T. and Y.O. wrote the manuscript with assistance from all authors.

Disclosure statement

No potential conflict of interest was reported by the authors.

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