Asymmetric Total Synthesis of a Beer-Aroma Constituent Based on Enantioconvergent Biocatalytic Hydrolysis of Trisubstituted Epoxides

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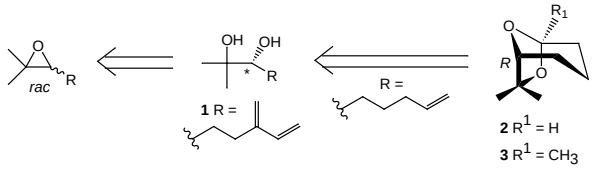
Abstract: A short asymmetric total synthesis of the plant constituent myrcenediol [(*R*)-**1**], and (*S*)-7,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**2**), which is a volatile constituent of the aroma of beer was accomplished via a chemoenzymatic protocol. The key step consisted of a biocatalytic hydrolysis of trisubstituted epoxides bearing olefinic side chains which proceeded in an enantioconvergent fashion, i.e., a single enantiomeric *vic*-diol was obtained from the racemate in up to 91% ee and 92% isolated yield.

Key words: epoxide hydrolase, enantioconvergent hydrolysis, trisubstituted epoxide, beer-aroma

Bacterial epoxide hydrolases have been shown to be highly versatile biocatalysts for the preparation of nonracemic *vic*-diols. In particular, sterically more demanding 2,2-disubstituted epoxides were hydrolyzed with excellent selectivities (E-values up to >200)[1] and for 2,3-disubstituted analogues, the biohydrolysis was shown to proceed in an enantioconvergent fashion, i.e., only a single stereoisomeric *vic*-diol was formed from the *rac*-epoxide in 100% theoretical yield.[2] Most recently, this phenomenon of enantio-convergence was also observed for trialkyl-oxiranes.[3] In order to apply this highly efficient method for the generation of nonracemic *vic*-diols to natural product synthesis, we investigated trisubstituted epoxides bearing olefinic side chains, which would serve as functional groups for further (oxidative) transformations. From our previous studies[4,5] it was anticipated that these lipophilic substrates would be well accepted by epoxide hydrolases. In this context, epoxides possessing a terpenoid structural framework seemed to be an attractive synthetic target.

Myrcenediol (**1**) is a plant constituent, which was isolated from the roots of *Bidens graveolens*[6] and from the flowers of *Tanacetum annuum*.[7] Neither its enantiomeric excess nor its absolute configuration was investigated. The (*R*)-enantiomer of **1**, which was synthesized via four steps from myrcene (**4a**) using Baker's yeast reduction of a ketone for the introduction of chirality, served as chiral building block for the synthesis of Hippospongic Acid A.[8]

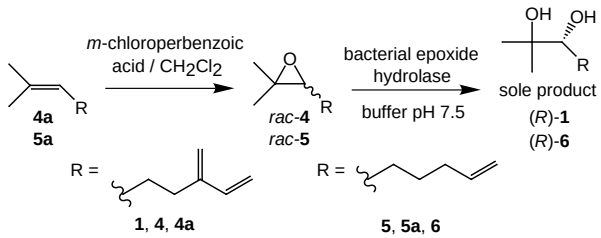
The (*S*)-enantiomer of 7,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**2**) is known as a volatile contributor to the aroma of beer[9] and was first isolated from Japanese hop oil.[10] Asymmetric synthesis of **2** was accomplished using tartaric acid as chiral starting material,[11] through resolution,[12] or via asymmetric cycloaddition employing Oppolzer's chiral sultam[13] and Sharpless dihydroxylation.[14] Retrosynthetic analysis showed that both of the target compounds are easily accessible via an enantioconvergent biocatalytic hydrolysis of trisubstituted epoxides bearing suitable olefinic side chains as the key step (Scheme 1).



Scheme 1 Retrosynthetic analysis

Epoxides *rac*-**4** and *rac*-**5** were prepared from commercially available alkenes **4a** and **5a** via chemoselective epoxidation of the electron-rich internal C=C bond using *m*-chloroperbenzoic acid in 83% yield (Scheme 2). The absence of spontaneous hydrolysis in aqueous buffer was verified for both substrates in the absence of biocatalyst and was shown to be negligible (<3%) within the anticipated reaction time of ~48 hours.

In order to find a suitable biocatalyst, *rac*-**4** and *rac*-**5** were screened for hydrolytic activity using resting cells of a range of pigment-producing bacteria which are known to possess epoxide hydrolase activity (Table 1). In each case, where activity was observed, the corresponding diol **1** or **6**, respectively, was the only detectable product.



Scheme 2 Synthesis of substrates and biocatalytic hydrolysis

Table 1 shows the stereoselectivities [given as conversion (c) and enantiomeric purities of substrate (ee_S) and product (ee_P)][15] obtained in the biohydrolysis of *rac*-**4** and *rac*-**5**. Substrate **4** was hydrolyzed with low to acceptable selectivities by several strains with the predominant forma-

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Table 1 Stereoselectivities from the Biocatalytic Hydrolysis of *rac*-**4** and *rac*-**5**

Entry		Substrate					
		4			**5**		
	Strain	Conversion[a] (%)	ee Epoxide	ee Diol	Conversion[b] (%)	ee Epoxide	ee Diol
1	*Rhodococcus ruber* DSM 44540	64	86 (*R*)	86 (*R*)	80	75 (*S*)	82 (*R*)
2	*Rhodococcus ruber* DSM 44539	46	85 (*R*)	60 (*R*)	82	64 (*S*)	82 (*R*)
3	*Rhodococcus ruber* DSM 44541	65	87 (*R*)	85 (*R*)	78	59 (*S*)	77 (*R*)
4	*Rhodococcus equi* IFO 3730	73	9 (*R*)	85 (*R*)	64	7 (*R*)	50 (*R*)
5	*Rhodococcus sp.* CBS 717.73	54	78 (*R*)	40 (*S*)	71	8 (*S*)	60 (*R*)
6	*Mycobacterium paraffinicum* NCIMB 10420	29	83 (*R*)	34 (*R*)	71	> 99 (*R*)	81 (*R*)
7	*Arthobacter sp.* DSM 312	10	7 (*S*)	14 (*R*)	4	3 (*R*)	44 (*S*)
8	*Streptomyces lavendulae* ATCC 55209	2	<1	22 (*R*)	6	5 (*R*)	96 (*R*)

[a]After 48 h.
[b]After 40 h.

tion of (*R*)-**1** in up to 86% ee, except for *Rhodococcus sp*. CBS 717.73, which produced the (*S*)-enantiomer (entry 5). Several data sets of c, ee_S and ee_P clearly indicated that the transformation does not follow a kinetic resolution pathway, which is most striking for entries 1, 3, 4 and 5.

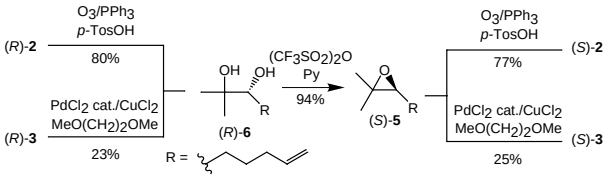
Similar results were obtained for substrate *rac*-**5**. Again, the formation of (*R*)-**6** was predominant with a single exception (*Arthobacter sp.* DSM 312, entry 7). The clear indication of a non-kinetic-resolution-type was even more evident for substrate *rac*-**5**, in particular for entries 1–6 and the possibility of an enantioconvergent transformation - as indicated by a high ee_P at conversion far beyond the 50%-benchmark - is evident for entries 1–3.

The mechanistic reason for this enantioconvergent pathway is the fact that both enantiomers are hydrolyzed with opposite regioselectivity, whereas the (*S*)-enantiomer of the oxirane is attacked by [OH^-] at the less substituted oxirane carbon atom with concomitant inversion of configuration, the (*R*)-enantiomer is transformed via retention through attack at the fully substituted oxirane carbon atom. Both pathways lead to the formation of an (*R*)-configurated diol from a *rac*-epoxide as the sole product.[3]

For preparative-scale biotransformations, *Rhodococcus ruber* DSM 44540 was chosen as the prime candidate, since it gave best selectivity for *rac*-**4** and was proven to be suitable towards upscaling.[16] Unfortunately, the most selective strain for substrate *rac*-**5** (*Streptomyces lavendulae* ATCC 55209) was hampered by insufficient reaction rates.

Thus, hydrolysis of *rac*-**4** (50 mg) using 0.2 g of resting cells of *Rhodococcus ruber* DSM 44540 in Tris-buffer (pH 8.0) gave 52 mg of (*R*)-Myrcenediol (**1**) in 92% yield and 83% ee as the sole product. The absolute configuration of **1** was determined by comparison with independently synthesized material.[8] The overall yield from alkene **4a** to (*R*)-**1** was 68%.

In a similar fashion, (*R*)-2-methyl-7-octene-2,3-diol (**6**) was obtained from *rac*-**5** (211 mg) using 1.0 g of lyophilized *Rhodococcus ruber* DSM 44540 cells in 90% yield and 90% ee. The unexpected higher enantiomeric excess of the product at elevated conversion (compare entry 1) can be attributed to the assumption that the slower reacting (*S*)-enantiomer of the epoxide is transformed with higher regioselectivity than the (*R*)-counterpart.[3] Oxidation of (*R*)-**6** by ozonolysis, followed by acid-catalyzed ring-closure in a one-pot reaction gave (*R*)-**2** in 80% yield and 95% ee (Scheme 3). The overall yield of the reaction sequence from alkene **5a** to (*R*)-**6** was 60%.



Scheme 3 Enantio-complementary chemoenzymatic synthesis of both enantiomers of bicyclic acetals **2** and **3**

Since no bacterial strain produced (*S*)-**6** in high ee - which is required for the synthesis of the naturally occurring (*S*)-enantiomer of **2** - the (*R*)-enantiomer was used as starting material instead. Inversion of the stereogenic center was achieved via an epoxide-closing-reopening sequence, which proceeded with inversion and retention of absolute configuration, respectively.[17–19] Thus, diol (*R*)-**6** (ee 95%) was transformed into the corresponding trifluoromethane sulfonate[20] followed by immediate ring-closure in the presence of base (3 equivalents of pyridine) to give (*S*)-**5** in 94% yield and 95% ee. In order to effect a stereochem-

ically 'clean' hydrolysis with complete retention of configuration under acidic conditions,[17–21] the crude product had to be purified. Best results were achieved using a THF–H_2O mixture (1:1) and H_2SO_4 as catalyst. Thus 80 mg of (*S*)-**5** (ee 95%) gave 71 mg of (*S*)-**6** in 79% yield and 92% ee, which indicated that only a trace amount of racemization took place. The overall yield for the inversion sequence was 74%. Ozonolysis followed by acid-catalyzed acetal formation of (*S*)-**5** gave (*S*)-**2** in 77% yield and 92% ee.

In order to show the flexibility of the method, both enantiomers of the desmethyl-analogue (**3**) of the hop-oil ingredient were synthesized via Wacker oxidation of **6** using $PdCl_2$ as catalyst, and $CuCl_2$ as reoxidant. Thus 490 mg of (*R*)-**6** were transformed into 110 mg of (*R*)-**3** (ee 93%). Analogous results were obtained for the (*S*)-enantiomer.

In conclusion, we have demonstrated that the enantioconvergent hydrolysis of trisubstituted epoxides bearing olefinic side chains using bacterial epoxide hydrolases proceeded in a highly selective manner, which provided the corresponding *vic*-diols in almost quantitative yield. The latter compounds were transformed into terpenoid natural products in nonracemic form in a straightforward manner.

NMR spectra were recorded in $CDCl_3$ using a Bruker AMX 360 at 360 MHz (^{1}H) and 90 MHz (^{13}C), or a Bruker DMX Avance 500 at 500 MHz (^{1}H) and 125 MHz (^{13}C). Chemical shifts are reported relative to TMS (δ = 0.00 ppm) with $CHCl_3$ as internal standard [δ = 7.23 (^{1}H) and 76.90 ppm (^{13}C)], coupling constants (*J*) are given in Hz. ^{13}C NMR multiplicities were determined by using a DEPT pulse sequence. TLC plates were run on silica gel Merck 60 (F_{254}) and compounds were visualized by spraying with vanillin/concd H_2SO_4 (5 g/L) (detection I), or by dipping into a $KMnO_4$ reagent [2.5 g/L $KMnO_4$ in H_2O] (detection II). Compounds were purified either by flash chromatography on silica gel Merck 60 (230–400 mesh) or, for volatile compounds, by Kugelrohr distillation. Petroleum ether (PE) with boiling range of 60–90 °C was used. GC analyses were carried out on a Varian 3800 gas chromatograph equipped with FID and either a HP1301 or a HP1701 capillary column (both 30 m, 0.25 mm, 0.25 μm film, N_2). Enantiomeric purities were analyzed using a CP-Chirasil-DEX CB column (25 m, 0.32 mm, 0.25 μm film) with H_2 as carrier gas. Solvents were dried and freshly distilled by common practice. For anhydrous reactions, flasks were dried at 150 °C and flushed with dry Ar just before use. Myrcene (**4a**, technical grade) and 7-methyl-1,6-octadiene (**5a**) were purchased from Aldrich. *m*-Chloroperbenzoic acid (70%, *m*-CPBA) from Fluka was used. Lyophilized bacterial cells were used for biotransformations. Bacteria were obtained from culture collections; the following strains (which were previously referred to the culture collection of the Institute of Biotechnology, Graz University of Technology), were classified and deposited at DSMZ (Braunschweig, Germany): *Nocardia* EH1 = *Rhodococcus ruber* SM 1789 = DSM 44540; *Nocardia* TB1 = *Rhodococcus ruber* SM 1790 = DSM 44539; *Nocardia* H8 = *Rhodococcus ruber* SM 1788 = DSM 44541; all strains were grown as previously described.[22–25]

Epoxidation of 4a and 5a to furnish 4 and 5; General Procedure

Alkene **4a** or **5a** (35 mmol) was dissolved in CH_2Cl_2 (300 mL) and cooled to 0 °C. K_2CO_3 (9.5 g, 68.7 mmol) and *m*-CPBA (70%, 10.0 g, 40.6 mmol) were added and the suspension was stirred for 3 h. After the reaction was complete, solids were filtered and the filtrate was treated with $Na_2S_2O_5$ (10%, 200 mL). After phase separation, the organic phase was washed with sat. $NaHCO_3$ (3 × 200 mL), dried and evaporated. Kugelrohr distillation yielded pure epoxides **4** and **5**, details and spectroscopic data are given below.

6,7-Epoxy-7-methyl-3-methylene-1-octene

Epoxidation of **4a** (3.0 g, 24.0 mmol) yielded after Kugelrohr distillation (43 mbar, 115–120 °C) **4** (2.81 g, 83%) as a colorless liquid. R_f (PE–EtOAc, 1:1) = 0.85 (detection II).

^{1}H NMR data were in full agreement with those previously reported.[26]

^{13}C NMR (90.55 MHz, $CDCl_3$): δ = 18.68, 24.76, 27.47, 28.30, 58.36, 63.98, 113.31, 116.03, 138.48, 145.34.

2,2-Dimethyl-3-pent-4-enyloxirane

Epoxidation of **5a** (2.0 g, 14.3 mmol) gave after Kugelrohr distillation (40 mbar, 125–30 °C) **5** (0.93 g, 83%) as a colorless liquid. R_f (PE–EtOAc, 1:1) = 0.78 (detection II); spectroscopic data were in full agreement with those previously reported.[27]

2-Methyl-6-methylene-7-octene-2,3-diol [(*R*)-1]

Lyophilized cells of *Rhodococcus ruber* DSM 44540 (0.2 g) were rehydrated in Tris-buffer (15 mL, pH 8.0, 50 mM) for 1 h and *rac*-**4** (50 mg, 1.5 mmol) was added in one portion. The mixture was incubated at 30 °C for 200 h with shaking at 130 rpm. The solution was extracted thrice with CH_2Cl_2 (10 mL), dried (Na_2SO_4) and concentrated. After flash chromatography, (*R*)-**1** (52 mg, 92%, ee 83%) was isolated as a colorless oil. R_f (PE–EtOAc, 1:1) = 0.36 (detection II); spectroscopic data were in full agreement with those previously reported.[28]

2-Methyl-7-octene-2,3-diol [(*R*)-6]

Lyophilized cells of *Rhodococcus ruber* DSM 44540 (1.0 g) were rehydrated in Tris-buffer (60 mL, pH 8.0, 50 mM) for 1 h and *rac*-**5** (211 mg, 1.5 mmol) was added in one portion. The mixture was incubated for 143 h at 30 °C. The solution was extracted 5 times with CH_2Cl_2 (40 mL), dried (Na_2SO_4) and concentrated. After flash chromatography (*R*)-**6** was isolated as a colorless oil (213 mg, 90%, ee 90%). R_f (PE–EtOAc, 1:1) = 0.32 (detection II); spectroscopic data were in full agreement with those previously reported.[14]

7,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane [(*S*)-2]

Diol (*S*)-**6** (30 mg, 0.19 mmol, ee 92%) was dissolved in anhyd CH_2Cl_2 (5 mL). The solution was cooled to –80 °C and O_3 was bubbled through until the blue color persisted. Excess O_3 was removed with a stream of Ar. PPh_3 (40 mg, 0.15 mmol) was added and the solution was allowed to warm to r.t. over 2 h. *p*-Toluenesulfonic acid (10 mg) was added and the solution was stirred overnight. The solution was washed with sat. $NaHCO_3$ (5 mL) and dried (Na_2SO_4). After concentration in vacuo at 0 °C, the crude product was purified by flash chromatography on silica gel (pentane–Et_2O, 95:5) to yield (*S*)-**2** (21 mg, 77%, ee 94%) as a colorless liquid. Spectroscopic data were in full agreement with those previously reported.[13]

$[\alpha]^{20}_D$ –79.96 (*c* 0.50, $CHCl_3$).

R_f (PE–EtOAc, 1:1) = 0.78, (detection I).

7,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane [(*R*)-2]

Diol (*R*)-**6** (270 mg, 1.7 mmol, ee 91%) was treated with O_3, PPh_3 and *p*-toluenesulfonic acid as described above to yield (*R*)-**2** (194 mg, 80%, ee 95%) as a colorless liquid. Spectroscopic data were identical to those of (*S*)-**2**.

$[\alpha]^{D}_{20}$+80.32 (*c* 0.64, $CHCl_3$).

5,7,7-Trimethyl-6,8-dioxabicyclo[3.2.1]octane [(*R*)-3]
Diol (*R*)-**6** (490 mg, 3.1 mmol, ee 91%) was dissolved in anhyd 1,2-dimethoxyethane (10 mL). The solution was stirred at r.t., $PdCl_2$ (0.10 g, 0.56 mmol) and $CuCl_2$ (0.58 g, 4.3 mmol) were added and stirring was continued for 12 h. The brown solution was diluted with H_2O and Et_2O (10 mL each). After phase separation, the aqueous layer was extracted twice with Et_2O (5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. After flash chromatography (pentane–Et_2O, 10:1), (*R*)-**3** (110 mg, 23%, ee 93%) was isolated as a colorless liquid.

R_f (PE–EtOAc, 1:1) = 0.84 (detection I).

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.29 (s, 3 H), 1.38 (s, 3 H), 1.43 (s, 3 H), 1.56–1.66 (m, 4 H), 1.89 (m, 2 H), 1.89 (s, 1 H).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 17.57, 21.35, 24.67, 26.27, 29.62, 34.61, 81.28, 81.56, 107.72.

5,7,7-Trimethyl-6,8-dioxabicyclo[3.2.1]octane [(*S*)-3]
Diol (*S*)-**6** (292mg, 1.8 mmol, ee 92%) was oxidized using the Wacker-oxidation procedure described above to yield (*S*)-**3** (71.4 mg, 25%, ee 96%). Spectroscopic data were identical to those of (*R*)-**3**.

Inversion Procedure for (*R*)-6 to (*S*)-6
Diol (*R*)-**6** (180 mg, 1.1 mmol, ee 91%) was dissolved in anhyd CH_2Cl_2 (5 mL) under Ar and pyridine (0.25 mL, 3.12 mmol) was added. The solution was cooled to 0 °C and trifluoromethanesulfonic anhydride (0.23 mL, 1.37 mmol) was added. After 1 h the solution was washed with 5% HCl (5 mL) and sat. $NaHCO_3$ (5 mL). The organic phase was dried (Na_2SO_4) and concentrated. After flash chromatography (pentane–Et_2O, 5:1), (*S*)-**5** (150 mg, 94%, ee 95%) was isolated as a colorless liquid. Epoxide (*S*)-**5** (80 mg, 0.57 mmol) was dissolved in THF–H_2O (1:1, 2 mL) and 6 N H_2SO_4 (2 drops) was added. The solution was stirred for 2 h and extracted twice with EtOAc (2 mL). The organic phase was washed with sat. $NaHCO_3$ (4 mL) and dried (Na_2SO_4). After flash chromatography (pentane–Et_2O, 2:1), (*S*)-**6** was isolated as a colorless oil in 74% overall yield (71 mg, ee 92%). Spectroscopic data were in full agreement with those previously reported.[14]

Synthesis of Reference Material for *rac*-Diols 1 and 6
Diols (±)-**1** and (±)-**6** were obtained by acid-catalyzed hydrolysis of the corresponding *rac*-oxiranes **4** and **5** (0.2 M in H_2O–THF, 1:1 containing 3–4 drops of 6 N H_2SO_4). Extractive workup and flash chromatography (PE–EtOAc, 5:1) gave pure diols (±)-**1** and (±)-**6**. Spectral data of these reference compounds matched those of material obtained from biotransformations and were in full agreement with those previously reported.[14]

Table 2 GC-Analyses of Enantiomeric Compositions

Compound	Conditions	t_R (min) (Absolute Config.)
1	12 psi He, 135 °C (iso)	6.53 (*S*), 6.79 (*R*)
2	12 psi He, 100 °C (iso)	4.25 (*R*), 4.32 (*S*)
3	20 psi He, 100 °C (iso)	2.34 (*R*), 2.45 (*S*)
4	12 psi He, 125 °C (iso)	18.12 (*R*), 18.60 (*S*)
6	12 psi H_2, 125 °C (iso)	3.32 (*S*), 3.48 (*R*)
5	12 psi H_2, 125 °C (iso)	6.60 (*S*), 6.92 (*R*)

Determination of Absolute Configuration

Absolute configurations of the biotransformation products were determined via co-injection with independently synthesized standard material on GC using a chiral stationary phase. Reference material was obtained as follows: Sharpless dihydroxylation of 2-methyl-2,7-octadiene using α-AD-mix[14] gave (*S*)-**4** (ee 87%).

Diol (*R*)-**1** was synthesized based on a procedure previously described:[8] Oxidation of *rac*-**1** (50 mg, 0.30 mmol) with pyridinium-SO_3 complex (150 mg, 0.94 mmol) in anhyd DMSO (3 mL) yielded 2-methyl-6-methylene-2-hydroxy-oct-7-en-3-one (30 mg, 61%).

R_f (PE–EtOAc, 5:1) = 0.59 (detection I).

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 5.01 (s, 1 H), 5.06 (s, 1 H), 5.11 (d, 1 H, *J* = 10.8 Hz), 5.29 (d, 1 H, *J* = 17.6 Hz), 6.38 (dd, 1 H, *J* = 17.6, 10.9 Hz).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 25.43, 26.51, 29.74, 34.45, 76.23, 113.72, 116.47, 138.30, 144.92, 213.77.

The latter material was reduced with Baker´s yeast to furnish (*R*)-**1** (ee 93%, yield 20%).

Screening of Biocatalysts for the Hydrolysis of 4 and 5; General Procedure
rac-Epoxides **1a**, **2a** and **3a** (5 μL) were hydrolyzed using rehydrated lyophilized cells (50 mg) in Tris-buffer (1 mL, 0.05 M, pH 8.0) by shaking the mixture at 30° C with 130 rpm. After 24 h and 48 h, aliquots of these solutions (0.5 mL) were extracted twice with EtOAc (0.5 mL each). To facilitate phase separation, the cells were removed by centrifugation. The combined organic layers were dried and analyzed by GC on a chiral stationary phase.

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