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Simple Resolution of Racemic Salicylic Aldehydes Having an Isobornyl Substituent

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Abstract: The resolution of the racemic salicylic aldehydes with isobornyl fragment **2** via diastereomer formation with (*R*)-1-phenylethylamine has been carried out.

Keywords: Enantiomeric resolution, salicylic aldehydes, Schiff bases, terpenoids, terpenylphenols

INTRODUCTION

Terpenylphenolic compounds are physiologically active substances with a wide range of activity and low toxicity. In particular, isobornylphenols are used for the local treatment of infection and inflammation of the throat.[1] Also, recently the isobornylphenol derivative was to have found antiplatetel and antithrombogenic activity.[2] Physiological activity and the possibility of using these derivatives for further synthesis requires development of methods for obtaining their optically active forms.

Alkylation of phenol or *p*-cresol with optically active camphene leads to racemic isobornylphenols **1a,b** (Fig. 1), which were formed as a result of Wagner–Meerwein cascade rearrangements. The racemic (±)**-1** have

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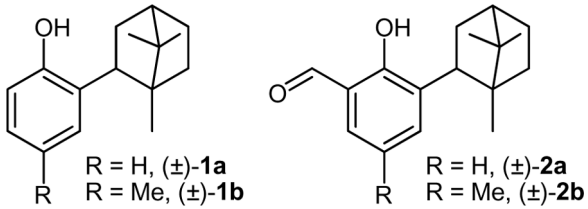


Figure 1. Racemic *o*-isobornylphenols **1** and their formylated derivatives **2**.

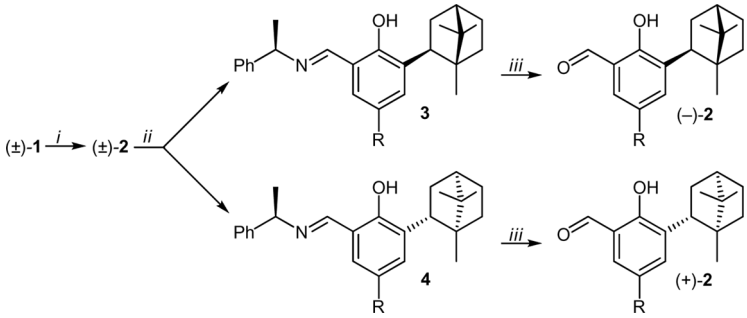
been previously prepared by alkylation of phenol or *p*-cresol by camphene with $(PhO)_3Al$ and $(4\text{-Me-PhO})_3Al$ as a catalysts.[3]

As far as we know, only a high-performance liquid chromatographic (HPLC) method has been used for the resolution of chiral alkylphenols. In all cases, the key stage is use of high-priced preparative columns. For example, Saito et al. reported the separation of *p*-nonylphenols isomers by chiral HPLC.[4] Berkessel et al. showed the resolution of (±)-**1b** using a Chiralcel OJ column.[5] In the same work, enantiomers of aldehyde **2b** were obtained by conversation into imines with (*R*)-phenylglycinol and HPLC resolution of diastereomeric imines following hydrolysis. Also, Schiff bases obtained from enantiomers **2b** were successfully applied as tridentate ligands with two elements of chitality in V-catalyzed asymmetric sulfoxidation.[6]

RESULTS AND DISCUSSION

We used a modified combination of the described method to separate (+)-**2** and (−)-**2**.[5] First, racemic aldehydes (±)-**2** were obtained by the formylation of racemic terpenylphenols (±)-**1** with formaldehyde in the presence of montmorillonite KSF clay with Et_3N.[7] Synthesis of (±)-**2** was achieved by refluxing at atmospheric pressure without using of an autoclave as described in the original method. This formylation leads to the salicylaldehyde (±)-**2** with good selectivity and moderate yields (Scheme 1).

The resolution of racemic aldehydes (±)-**2** were realized through Schiff base formation of (±)-**2** by reaction with commercially available (*R*)-1-phenylethylamine. Diastereomers **3** and **4** were obtained with 68–76% yield and 74–98% *de* by fractional crystallization from pentane. Finally, the enantiomeric enriched aldehydes (+)-**2** and (−)-**2** were liberated via acid hydrolysis of the **3** and **4** with good yields and moderate to good *ee* values (see Table 1).



Scheme 1. Reagents and conditions: (*i*) (a) HCHO, montmorillonite KSF, Et_3N, toluene, reflux at Ar atmosphere, 15 h, then chromatography on silica gel; (*ii*) (a) (*R*)-1-phenylethylamine, 4 Å MS, toluene, reflux at Ar atmosphere, 3.5 h; (b) Crystallization from pentane; (*iii*) aq. HCl (37%), EtOH, rt, 6 h, then chromatography on silica gel.

In summary, we report a simple procedure for preparation of enaniomers of salicylaldehydes having an isoborhyl fragment.

EXPERIMENTAL

General

The infrared (IR) spectra were recorded on a Shimadzu IR Prestige 21 Fourier-transform spectrometer in KBr pellets. The ^1H and ^{13}C NMR spectra were measured on Bruker Avance II 300 (300 MHz and 75 MHz) in $CDCl_3$. The assignment of the signals was made using ^{13}C APT experiments. The melting points were measured on a Kofler hot-stage apparatus. Specific rotations were measured on a Kruss Optronic P3002RS polarimeter. The course of the reactions was monitored by thin-layer chromatography (TLC) on Sorbfil plates using hexane–Et_2O

Table 1. Resolution of racemic aldehydes **2** via diastereomeric imines **3** and **4**

Entry	R	Imine	Yield (%)	*De* (%)[a]	Aldehyde	Yield (%)	*Ee* (%)[b]
1	H	**3a**	58	98	**(−)-2a**	97	98
2	H	**4a**	60	74	**(+)-2a**	96	72
3	4-Me	**3b**	76	91	**(−)-2b**	98	92
4	4-Me	**4b**	68	98	**(+)-2b**	97	96

[a]Determined by GC.
[b]Determined by HPLC.

solvent systems. To detect the compounds, the plates were treated with a $KMnO_4$ solution (15 g of $KMnO_4$, 300 mL of H_2O, and 0.5 mL of concentrated H_2SO_4). Toluene was dried over $CaCl_2$ and distilled over sodium metal. Pentane and hexane were freshly distilled. Paraformaldehyde was of reagent-grade quality. Column chromatography used silica gel (70/230 μ, wet packed). Commercially available *R*-(+)-1-phenylethylamine (Alfa Aesar, ChiPros® 99 + %, 99 + % *ee*) were employed without purification. Molecular sieves (4 Å) and montmorillonite KSF (Acros) were used after heating for 6 h at 130°C and 3 h at 140°C, respectively.

Racemic Salicylic Aldehydes (±)-2

A solution of the phenol (±)-**1** (20 mmol), paraformaldehyde (80 mmol), triethylamine (20 mmol), and montmorillonite KSF (3 g) in toluene (30 mL) was heated at 100°C under efficient stirring and Ar atmosphere. After 15 h, the reaction mixture was cooled to room temperature, and the catalyst was filtered and washed with Et_2O. The excess of solvent was removed at reduced pressure. The reaction mixture was separated over a column (silica gel, 70/230μ, hexane/Et_2O, 75:1 → 20:1) to afford corresponding aldehyde (±)-**2**.

Data

Rac-2-Hydroxy-3-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl) benzaldehyde (±)-**2a**

Yield 60%. Yellowish solid; mp 67–68. Anal. calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.07; H, 8.52.

Rac-2-Hydroxy-5-methyl-3-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl) benzaldehyde (±)-**2b**

Yield 71%. Yellow solid; mp 100–101. Anal. calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.33; H, 8.84.

Spectral characteristics of the compounds (±)-**2a** and (±)-**2b** are consistent with those described previously.[5,8]

Synthesis of Schiff Bases as Diastereomeric Mixtures 3 and 4

The solution of aldehyde (±)-**2** (7.7 mmol) and *R*-(+)-1-phenylethylamine (7.7 mmol) in 30 mL of anhydrous toluene was stirred at reflux under an

Ar atmosphere for 3.5 h. After filtration from molecular sieves, the solvent was removed under reduced pressure to yield a mixture of diastereomeric Schiff bases **3** and **4** (100% yield), which were separated by fractional crystallization from pentane.

Diastereomeric excess (*de*) of **3** and **4** were determined by gas chromatography [GC; Supelco SPB^{TM}-35 column, 30 m × 0.32 mm × 0.25 μm, 255°C (isothermic): t(**3a**) = 21.6 min, t(**4a**) = 20.7 min; t(**3b**) = 22.1 min, and t(**4b**) = 23.1 min].

Data

2-(((*R*)-1-Phenylethylimino)methyl)-6-((1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol **3a**

Yield 58%. Yellow solid; mp 118–119°C (from pentane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.79 (s, 3H), 0.85 (s, 3H), 0.92 (s, 3H), 1.33–1.43 (m, 1H), 1.56–1.68 (m, 6H), 1.81–1.93 (m, 2H), 2.10–2.19 (m, 1H), 3.40 (t, 1H, *J* = 9.0 Hz), 4.56 (q, 1H, *J* = 6.6 Hz), 6.84 (m, 1H), 7.08 (d, 1H, *J* = 7.2 Hz), 7.25–7.42 (m, 6H), 8.42 (br.s, 1H), 13.90 (br.s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.86, 160.48, 144.02, 132.00, 130.78, 128.87, 128.64, 127.17, 126.43, 117.55, 117.98, 68.43, 49.85, 47.94, 45.74, 44.63, 39.83, 34.25, 27.53, 25.03, 21.41, 20.49, 12.39. IR (KBr, cm^{-1}): 3439 (OH); 1626 (C=N). Found (%): C, 83.03; H, 8.66; N, 3.90; calc. for $C_{25}H_{31}NO$ (%): C, 83.06; H, 8.64; N, 3.87.

2-(((*R*)-1-Phenylethylimino)methyl)-6-((1*S*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol **4a**

Yield 60%. Yellow solid; mp 92–93°C (from pentane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3H), 0.87 (s, 3H), 0.93 (s, 3H), 1.34–1.43 (m, 1H), 1.56–1.68 (m, 6H), 1.79–1.92 (m, 2H), 2.11–2.18 (m, 1H), 3.41 (t, 1H, *J* = 9.0 Hz), 4.56 (q, 1H, *J* = 6.6 Hz), 6.84 (m, 1H), 7.08 (d, 1H, *J* = 7.2 Hz), 7.25–7.40 (m, 6H), 8.41 (br.s, 1H), 13.87 (br.s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.93, 160.49, 143.96, 131.93, 130.78, 128.87, 128.61, 127.16, 126.44, 117.53, 118.05, 68.48, 49.86, 47.96, 45.74, 44.54, 39.77, 34.18, 27.52, 24.90, 21.44, 20.45, 12.34. IR (KBr, cm^{-1}): 3437 (OH); 1628 (C=N). Found (%): C, 83.02; H, 8.71; N, 3.88; calc. for $C_{25}H_{31}NO$ (%): C, 83.06; H, 8.69; N, 3.87.

4-Methyl-2-(((*R*)-1-phenylethylimino)methyl)-6-((1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol **3b**

Yield 76%. Yellow solid; mp 110–112°C (from pentane). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.79$ (s, 3H), 0.86 (s, 3H), 0.92 (s, 3H), 1.27–1.42 (m, 1H), 1.55–1.66 (m, 6H), 1.81–1.93 (m, 2H), 2.11–2.20 (m, 1H), 2.29 (s, 3H), 3.38 (t, 1H, $J = 9.0$ Hz), 4.55 (q, 1H, $J = 6.6$ Hz), 6.88 and 7.19 (both d, each 1H, $J = 0.9$ Hz, $J = 1.2$ Hz), 7.27–7.41 (m, 5H), 8.37 (br.s, 1H), 13.65 (br.s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 163.86$, 158.20, 144.12, 131.84, 131.66, 128.83, 128.62, 126.28, 127.13, 126.46, 117.63, 68.45, 49.84, 47.96, 45.74, 44.59, 39.78, 34.15, 27.52, 25.07, 21.43, 20.79, 20.48, 12.35; IR (KBr, cm^{-1}): 3420 (OH); 1632 (C=N). Found (%): C, 83.16; H, 8.88; N, 3,.70; calc. for $C_{26}H_{33}NO$ (%): C, 83.15; H, 8.86; N, 3.73.

4-Methyl-2-(((*R*)-1-phenylethylimino)methyl)-6-((1*S*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)phenol **4b**

Yield 68%. Yellow solid; mp 111–113°C (from pentane). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.83$ (s, 3H), 0.87 (s, 3H), 0.93 (s, 3H), 1.33–1.42 (m, 1H), 1.56–1.66 (m, 6H), 1.81–1.93 (m, 2H), 2.07–2.19 (m, 1H), 2.29 (s, 3H), 3.38 (t, 1H, $J = 9.2$ Hz), 4.55 (q, 1H, $J = 6.6$ Hz), 6.87 and 7.19 (both d, each 1H, $J = 1.8$ Hz, $J = 1.8$ Hz), 7.22–7.39 (m, 5H), 8.36 (br.s, 1H), 13.61 (br.s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 163.93$, 158.22, 144.05, 131.82, 131.59, 128.84, 128.58, 126.27, 127.11, 126.45, 117.62, 68.48, 49.85, 47.98, 45.73, 44.50, 39.73, 34.10, 27.51, 24.91, 21.46, 20.78, 20.45, 12.34; IR (KBr, cm^{-1}): 3422 (OH); 1632 (C=N). Found (%): C, 83.11; H, 8.90; N, 3.69; calc. for $C_{26}H_{33}NO$ (%): C, 83.15; H, 8.86; N, 3.73.

Absolute configurations of the imines were assigned by comparison of their optical rotation with literature data of aldehydes (+)-**2b** and (−)-**2b** obtained after hydrolysis reaction (see Ref. 5). The (*R*/*S*) configuration of **3a** and **4a** was given by analogy with the (*R*/*S*) configuration of diastereomers of compounds **3b** and **4b**.

Enantiomeric Enriched Salicylic Aldehydes (+)-2 and (−)-2

HCl (37%, 7 mL) was added to solution of diastereomeric enriched imine **3** or **4** (0.5 g) in ethanol (EtOH; 5 mL). The mixture was stirred at room temperature for 6 h. The excess solvent was removed at reduced pressure, and the residue was diluted with CH_2Cl_2 (75 mL). The organic layer was

washed with water (3×30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure and the residue was purified by chromatography (silica gel, 70/230 μ, hexane/Et_2O, 75:1) to afford corresponding enantiomer of aldehyde (+)-**2** and (−)-**2**.

Enantiomeric excesses of (−)-**2a** and (+)-**2a** were determined by HPLC with a Chiralcel OJ-H column (hexane/*i*-PrOH 200/1, 1.0 mL/min, 224 nm; t(−)-**2a** = 4.54 min, t(+)-**2a** = 6.08 min). Enantiomeric excesses of (−)-**2b** and (+)-**2b** were determined by HPLC with a Chiralpak AD column (hexane/*i*-PrOH 200/1, 0.5 mL/min, 224 nm; t(−)-**2b** = 8.22 min, t(+)-**2b** = 9.02 min).

Data

2-Hydroxy-3-((1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl) benzaldehyde (−)-**2a**

Yield 97%. Yellowish solid, $[\alpha]_D^{22} = -87.6$ ($c = 0.6$, $CHCl_3$); mp 86–88°C (from pentane).

2-Hydroxy-3-((1*S*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl) benzaldehyde (+)-**2a**

Yield 98%. Yellowish solid, $[\alpha]_D^{22} = +55.1$ ($c = 0.5$, $CHCl_3$); mp 88–90°C (from pentane).

2-Hydroxy-5-Methyl-3-((1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)benzaldehyde (−)-**2b**

Yield 98%. Yellowish solid, $[\alpha]_D^{22} = -40.9$ ($c = 0.6$, $CHCl_3$); mp 108–110°C (from pentane).

2-Hydroxy-5-Methyl-3-((1*S*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)benzaldehyde (+)-**2b**

Yield 97%. Yellowish solid, $[\alpha]_D^{22} = +41.0$ ($c = 0.6$, $CHCl_3$); mp 109–110°C (from pentane).

Absolute configurations of **2b** were assigned by comparison of their optical rotation with literature data.[5] The (*R*/*S*) configuration of (+)-**2a** and (−)-**2a** was given by analogy with the (*R*/*S*) configuration of enantiomers of compound **2b**.

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