Synthesis and Configurational Assignment of Chiral Salicylic Aldehydes: Novel Building Blocks for Asymmetric Catalysis

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Dedicated to Professor Dr. Dr. h.c. Waldemar Adam on the occasion of his 65th birthday

Keywords: Aldehydes / Asymmetric catalysis / Chiral auxiliaries / Electrophilic substitution / Schiff bases

We report the synthesis of three novel and chiral salicylic aldehyde building blocks **6**–**8**, each in both enantiomerically pure forms. Two of these salicylic aldehydes were prepared from (+)-camphene and each bear a [2.2.1]bicycloheptyl substituent *ortho* to the salicylic hydroxy group. In the third case, the chiral element at the 6-position is a (1-phenylethyl) group. The synthetic sequences consisted of *ortho*-alkylation of *para*-cresol with either camphene or styrene and subsequent *ortho*-formylation of the product phenols. The chromatographic separation of enantiomers was accomplished through the diastereomeric imines obtained from condensation of the racemic salicylic aldehydes with (*R*)-phenylglycinol. Finally, the absolute configurations of two of the salicylic aldehydes were established by X-ray crystallography. For this purpose, the (1-phenylethyl)-substituted salicylic aldehyde was condensed with L-valinamide, and the relative configuration of the resulting Schiff base diastereomer **12** was determined. In the second case, the racemic intermediate phenol *rac*-**15** was separated by HPLC on a chiral stationary phase, *ortho*-brominated, and analyzed by anomalous X-ray scattering.

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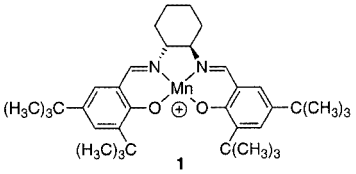
Introduction

Chiral Schiff bases play extremely important roles as ligands in metal-mediated asymmetric catalysis. The most prominent examples are the manganese-salen complexes introduced by Jacobsen and Katsuki for the asymmetric epoxidation of olefins, or their use as ligands for chiral Lewis acids, for the enantioselective opening of *meso*- or racemic epoxides, for example.[1,2] In most cases the overall chirality of the Schiff base complexes is due to chirality in the diamine component, such as, for example, in the case of the manganese complex **1**.[3] Introduction of a second element of chirality in the form of a chiral salicylic aldehyde gives rise to diastereomeric ligands/complexes. The "matched" diastereomer of these materials should be expected to afford even better enantioselection, whereas the "mismatched" diastereomer should perform worse.[4] This concept of "matched/mismatched" salen-ligands has been exploited in particular by Katsuki et al., as exemplified by the ruthenium complex **2**.[5]

Simple 1:1 adducts of salicylic aldehydes and chiral, amino acid-derived 1,2-amino alcohols have found use in the vanadium-catalyzed asymmetric sulfoxidation of thioethers.



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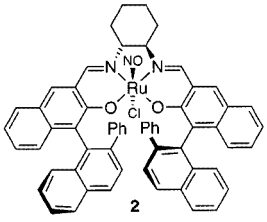

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For example, the ligand **3** was shown by Bolm et al. to induce an enantiomeric excess of 70% in the V-catalyzed oxidation of thioanisole (Scheme 1).[6] We reasoned that in troduction of a chiral salicylic aldehyde moiety might also further increase the selectivity of the chiral catalyst in this case. As reported earlier, we synthesized the Schiff bases **4** and **5**, and assessed their performance as ligands in V-catalyzed asymmetric sulfoxidations.[7] As expected, the sulfoxides were indeed obtained in higher enantiomeric purities (Scheme 1). The preparation of the axially chiral, binaphthyl-derived building block present in **4** was first reported by Katsuki et al.[8] Here we report the synthesis of the enantiomerically pure chiral salicylic aldehydes **6**−**8**, as well as their enantiomers *ent*-**6**−**8**, together with the configurational assignments of **6**/*ent*-**6** and **7**/*ent*-**7**. We are confident that chiral salicylic aldehydes of this type will prove beneficial for many other catalytic asymmetric transformations.

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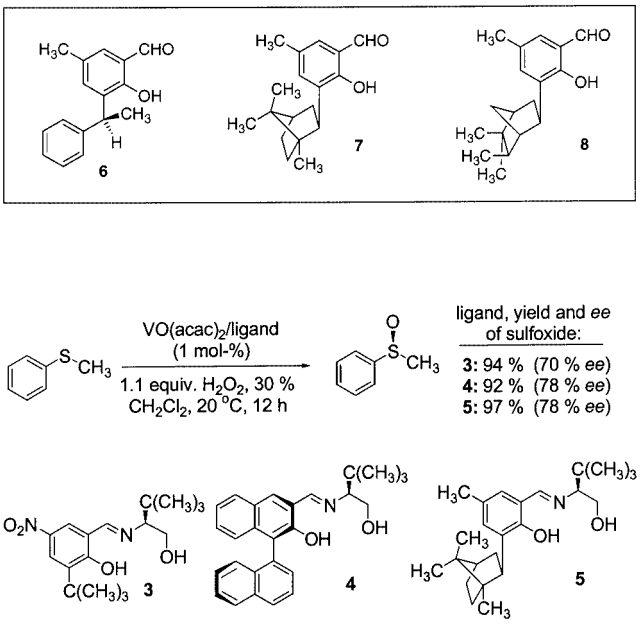


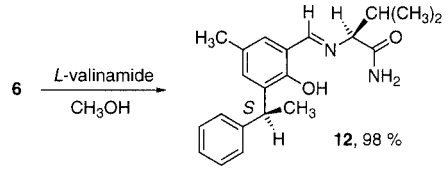
Scheme 1

Results

(1-Phenylethyl)-Substituted Salicylic Aldehydes 6/*ent*-6

Our synthesis of the aldehydes **6** and *ent*-**6** began with the known acid-catalyzed *ortho*-alkylation of *para*-cresol with styrene (Scheme 2), affording the racemic phenol *rac*-**9** in good yield.[9] *ortho*-Formylation according to Casiraghi et al. provided the salicylic aldehyde *rac*-**6**.[10] For the separation of enantiomers, *rac*-**6** was treated with (*R*)-phenylglycinol **10**.[11] The resulting diastereomeric imines **11a** and **11b** were separated by preparative HPLC on silica. Acid-catalyzed hydrolysis of the imines **11a** and **11b** afforded the enantiomerically pure aldehydes **6** and *ent*-**6**, respectively (Scheme 2).

For the assignment of configuration, the aldehyde **6** was derivatized with L-valinamide, affording the crystalline imine **12** (Scheme 3). X-ray crystallography of **12** (Figure 1) unambiguously established the *S* configuration in the salicylic aldehyde **6**.



Scheme 3

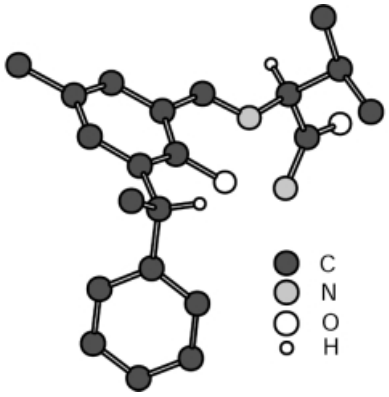
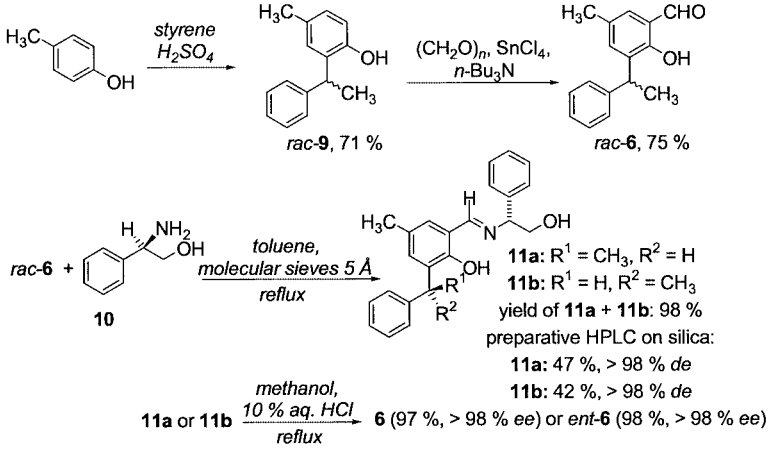


Figure 1. X-ray crystal structure of the imine **12**

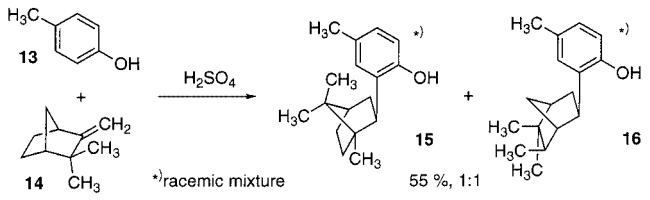
Isobornyl- and Camphenyl-Substituted Aldehydes 7, 8, *ent*-7, and *ent*-8

The first step in our synthesis of the isobornyl- or camphenyl-substituted salicylic aldehydes **7**, *ent*-**7**, **8**, and *ent*-**8** was the acid-catalyzed addition of (+)-camphene **14** to *p*-cresol **13** (Scheme 4).[12] With the well known camphenyl-isobornyl rearrangement in mind, we expected to obtain the racemic (2-isobornyl)cresol *rac*-**15**.[13] However, chromatographic workup of our reaction mixture revealed that *two* alkylated cresols had been produced in racemic form and



Scheme 2

in a 1:1 ratio: namely *rac*-**15** and *rac*-**16** (Scheme 4). The structural assignments of the product phenols were based on X-ray crystal structures determined for *rac*-**15** and *rac*-**16** (Figure 2).



Scheme 4

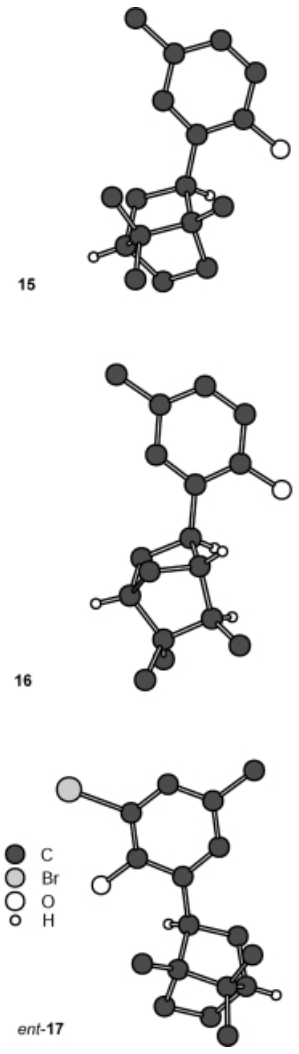
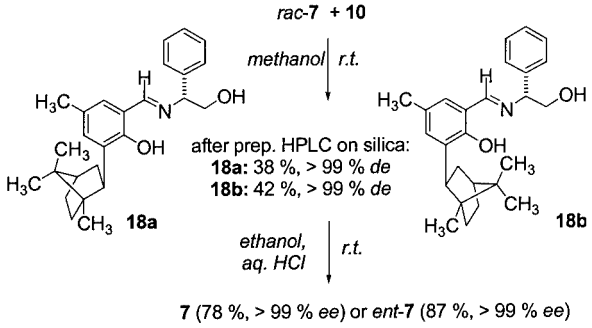


Figure 2. X-ray crystal structures of the phenols *rac*-**15**, *rac*-**16**, and *ent*-**17** (only one enantiomer shown for *rac*-**15**/**16**)

The racemic mixtures *rac*-**15** and *rac*-**16** were separated into their pure enantiomers by preparative HPLC on Chiralcel OJ. For the assignment of absolute configuration, the dextrorotatory phenol *ent*-**15** was treated with bromine, affording the crystalline *ortho*-bromophenol *ent*-**17** (89%). This proved suitable for X-ray crystallography, including the determination of absolute configuration by anomalous X-ray scattering (Figure 2). The configuration of the (−)-enantiomer **15** was established as 1*S*, as shown in Scheme 4.

For the preparation of the enantiomerically pure salicylic aldehydes **7** and *ent*-**7** on larger scales, the separation of the enantiomers of the intermediate phenol *rac*-**15** by preparative HPLC on chiral phase with subsequent Casiraghi formylation proved tedious, and so the synthetic sequence summarized in Scheme 5 was elaborated. Firstly, the racemic phenol *rac*-**15** was formylated to provide the racemic aldehyde *rac*-**7** (71%).[10] Treatment of this racemate with (*R*)-phenylglycinol (**10**)[11] resulted in the formation of the diastereomeric imines **18a** and **18b**. These could easily be separated by preparative HPLC on silica. Finally, acid-catalyzed hydrolysis of the separated imines **18a** and **18b** liberated the enantiomerically pure salicylic aldehydes **7** and *ent*-**7**.



Scheme 5

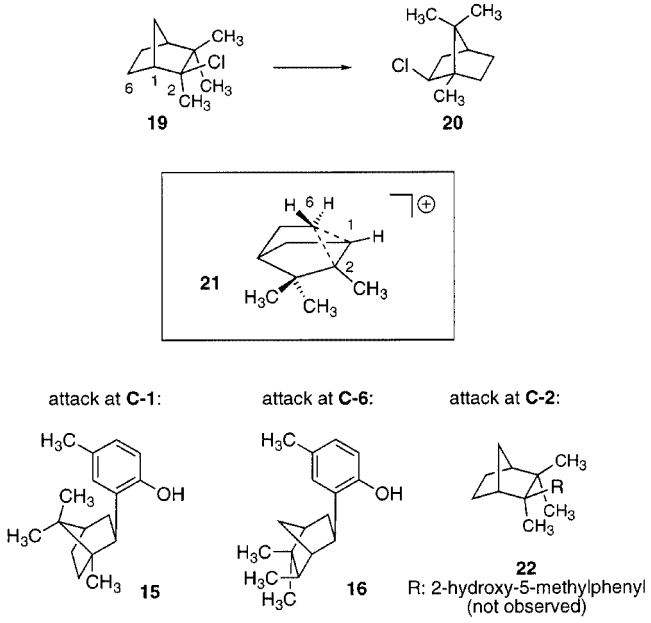
Formylation of the separated enantiomeric phenols **15** and *ent*-**15** (vide supra) enabled us to assign absolute configurations to the salicylic aldehydes **7** and *ent*-**7** obtained by hydrolysis of the imines **18a** and **18b** (comparison of optical rotation and HPLC coinjection on Chiralcel OJ). Consequently, the relative and absolute configurations of the diastereomeric imines **18a** and **18b** were also established.

The analogous chromatographic separation of the racemate *rac*-**8** through the diastereomeric imines derived from treatment with (*R*)-phenylglycinol (**10**)[11] proved not to be viable. Nevertheless, both the racemate *rac*-**16** and the individual phenols **16** and *ent*-**16** (from the small-scale separation of *rac*-**16** on Chiralcel OJ) could be converted into the corresponding salicylic aldehydes *rac*-**8**, **8**, and *ent*-**8**, respectively, by Casiraghi formylation.[10] No assignment of absolute configuration was carried out for the separated phenols **16**/*ent*-**16** or the aldehydes **8**/*ent*-**8**. Consequently, the configurations shown for the aldehyde **8** and for the phenol **16** in Scheme 1 and Scheme 4 have been chosen arbitrarily.

Discussion

The acid-catalyzed alkylation of *para*-cresol with styrene proceeded with the expected Markovnikov regioselectivity

and thus provided access to the chiral skeleton of the salicylic aldehydes **6** and *ent*-**6**. Clearly, the addition product was formed as a racemic mixture (*rac*-**9**). The analogous addition of (+)-camphene requires more detailed comment. It has been known for decades that the generation of the 2-camphenyl cation and subsequent trapping with nucleophiles usually gives rise to products with a camphenyl- or an isobornyl skeleton. Probably the most prominent example is the rearrangement of camphenyl chloride **19** to isobornyl chloride **20** (Scheme 6), studied as early as the 1920s by Meerwein et al.[13] Terpene rearrangements of this type are usually accompanied by at least partial, and in many cases complete, racemization.[14] For the 2-camphenyl cation, the most prominent pathway for racemization is an *exo*-2,3-methyl shift.[15] By our current mechanistic understanding, the bridged cation **21** accounts for the product structures observed experimentally.[16] Firstly, attack of a nucleophile at C-2 would give rise to *exo*-products incorporating the unrearranged (2-camphenyl) skeleton, whereas attack at C-1 would provide access to the isobornyl variants. Clearly, a reversible 1,2-hydrogen shift between positions 6 and 1 of the bridged cation **21** would result in racemization as well.[15] Finally, a 1,2-H-shift from C-6 to C-2 and subsequent attack of a nucleophile at C-6 could give rise to an *exo*-(5-camphenyl) product. In our case, the products resulting from the attack of *para*-cresol on C-1 (i.e., *rac*-**15**) and on C-6 (i.e., *rac*-**16**) were formed in equal amounts (Scheme 4, Scheme 6). However, the (2-camphenyl)-cresol **22** that would result from attack at C-2 was not observed as a product in our experiments. It may be argued either that the attack of the nucleophile (*para*-cresol) on the "tertiary position" of the cation **21** was disfavored for steric reasons, or that the charge density at this "tertiary position" was too low for efficient electrophilic attack on the aromatic substrate.



Scheme 6

Conclusion

In summary, we present the synthesis of three novel chiral salicylic aldehydes, each in both enantiomeric forms (i.e., **6**, *ent*-**6**, **7**, *ent*-**7**, **8**, *ent*-**8**). These aldehydes have already proven their potential in asymmetric catalysis, namely as building blocks for ligands used in the asymmetric sulfoxidation of prochiral thioethers.[7] It is to be expected that their incorporation into other Schiff base catalysts, originally based on chiral amines and achiral salicylic aldehydes, should also result in improved enantioselectivities.

Experimental Section

General: All solvents and organic substances were purified by standard methods. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded at ambient temperature in deuterated chloroform ($CDCl_3$). Melting points are corrected. Analytical thin layer chromatography was performed on 0.25 mm POLYGRAM Sil G/UV plates (Macherey−Nagel). Column chromatography was performed on 230 − 400 mesh silica gel (Macherey−Nagel).

(*RS*)-4-Methyl-2-(1-phenylethyl)phenol (*rac*-9): A solution of styrene (52.0 g, 500 mmol, 1.00 equiv.) in toluene (400 mL) was added dropwise over 2 h, at 100 °C under nitrogen, to a mixture of *p*-cresol (108 g, 1.00 mol, 2.00 equiv.) and conc. sulfuric acid (10.0 g, 100 mmol, 0.20 equiv.). The mixture was heated under reflux for 5 h and allowed to cool to room temperature. Water (400 mL) was added, and the mixture was extracted with diethyl ether. The organic layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure to provide the desired product (75.4 g, 355 mol, 71%) as a colorless oil after distillation (130 °C, 0.70 mbar). R_f = 0.30 (silica gel, toluene). ^{1}H NMR (300 MHz, $CDCl_3$, room temp.): δ = 1.69 (d, *J* = 7.2 Hz, 3 H), 2.36 (s, 3 H), 4.42 (q, *J* = 7.2 Hz, 1 H), 4.62 (s, br.), 1 H), 6.69 (d, *J* = 8.1 Hz, 1 H), 6.98 (dd, *J* = 8.1, *J* = 2.2, 1 H), 7.12 (d, *J* = 2.2 Hz, 1 H), 7.23−7.41 (m, 5 H) ppm. ^{13}C{^{1}H} NMR (75 Hz, $CDCl_3$, room temp.): δ = 20.9, 21.1, 38.8, 116.0, 126.5, 127.6, 128.0, 128.6, 130.1, 131.9, 145.6, 151.1 ppm. IR (film): $\tilde{\nu}$ = 3535 cm^{-1}, 3026, 2967, 2930, 2874, 1601, 1506, 1496, 1256, 1195, 811, 700. $C_{15}H_{16}O$ (212.29): calcd. C 84.86, H 7.60; found C 84.83, H 7.47.

(*RS*)-2-Hydroxy-5-methyl-3-(1-phenylethyl)benzaldehyde (*rac*-6): Tin(IV) chloride (547 mg, 2.10 mmol, 0.10 equiv.) and paraformaldehyde (1.46 g, 48.6 mmol, 2.20 equiv.) were added in small portions at room temperature to a solution of the phenol *rac*-**9** (4.46 g, 21.1 mmol, 1.00 equiv.) and tri-*n*-butylamine (1.56 g, 8.40 mmol, 0.40 equiv.) in toluene (40 mL). The mixture was heated under reflux for 8 h. After cooling to room temperature, the reaction mixture was poured onto 100 g ice and acidified to pH 2 with 2 N hydrochloric acid. The aqueous layer was extracted with diethyl ether (3 × 50 mL). The extract was dried over sodium sulfate and the solvent was removed under reduced pressure. Purification of the crude product by chromatography (silica gel, dichloromethane) afforded 3.80 g (15.8 mmol, 75%) of the aldehyde *rac*-**6** as pale yellow crystals. R_f = 0.55 (silica gel, toluene); m.p. 53 °C (methanol). ^{1}H NMR (300 MHz, $CDCl_3$, room temp.): δ = 1.62 (d, *J* = 7.3 Hz, 3 H), 2.30 (s, 3 H), 4.61 (q, *J* = 7.2 Hz, 1 H), 7.15−7.32 (m, 7 H), 9.82 (s, 1 H), 11.19 (s, 1 H) ppm. ^{13}C{^{1}H} NMR (75 Hz, $CDCl_3$, room temp.): δ = 20.6, 36.7, 120.1, 126.1, 127.7, 128.4, 128.7, 131.5, 134.9, 136.2, 145.3, 157.1. 196.7 ppm. IR (KBr pellet, cm^{-1}) 3500−3100, 3085, 3060, 3026, 2968, 2932, 2840, 1654, 1618, 1602,

1495, 1259, 1236, 699. $C_{16}H_{16}O_2$ (240.30): calcd. C 79.96, H 6.72; found C 79.81, H 6.82.

[*R*-(*R,*S**)]- and [*R*-(*R**,*R**)]-β-{[[2-Hydroxy-5-methyl-3-(1-phenylethyl)phenyl]methylene]amino}phenylethanol (11a and 11b):** The aldehyde *rac*-**6** (1.79 g, 7.45 mmol) and (*R*)-phenylglycinol **10** (1.02 g, 7.45 mmol) were dissolved in toluene (25 mL) under nitrogen, and molecular sieves (5 Å, 6.00 g) were added. The mixture was heated under reflux for 5 h. The molecular sieves were removed by filtration and washed with toluene. The organic phases were collected, and the solvent was removed under reduced pressure. Purification of the crude product by chromatography (silica gel, dichloromethane, 2-propanol; 50:1) afforded a mixture of the diastereomers **11a** and **11b** (2.62 g, 7.29 mmol, 98%). The diastereomers **11a** and **11b** were separated by preparative HPLC (LiChrosorb® Si-60; dichloromethane/2-propanol, 600:1, 80 mL/min). Separation of 2.50 g (6.95 mmol) of the mixture afforded the imines **11a** (1.18 g, 3.29 mmol, 47%, >98% *de*) and **11b** (1.04 g, 2.89 mmol, 42%, >98% *de*) as yellow oils.

The diastereomeric purities of the imines **11a** and **11b** were established by analytical HPLC (LiChrosorb® Si-60; dichloromethane/2-propanol, 100:1, 1 mL/min).

Imine 11a: $R_f = 0.25$ (silica gel, dichloromethane). ^{1}H NMR (300 MHz, $CDCl_3$, room temp.): δ = 1.61 (d, *J* = 7.2 Hz, 3 H), 1.83 (s, br.), 1 H), 2.26 (s, 3 H), 3.88 (ψd, *J* = 6.6 Hz, 2 H), 4.43 (ψt, *J* = 6.6 Hz, 1 H), 4.66 (q, *J* = 7.2 Hz, 1 H), 6.94 (d, *J* = 1.1 Hz, 1 H), 7.07 (d, *J* = 1.1 Hz, 1 H), 7.15−7.41 (m, 10 H), 8.42 (s, 1 H), 13.27 (s, br.), 1 H) ppm. ^{13}C{^{1}H} NMR (75 Hz, $CDCl_3$, room temp.): δ = 20.5, 20.9, 36.9, 67.6, 75.9, 118.0, 125.8, 127.1, 127.5, 127.7, 127.8, 128.2, 128.8, 129.8, 131.8, 133.9, 139.4, 146.1. 156.2, 166.6 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3574 cm^{-1}, 3412, 3083, 3060, 3026, 2965, 2930, 2872, 1630, 1600, 1493, 1461, 1451, 1262, 1238, 699. HRMS *m*/*z* = 359.1880 (60.9%, $C_{24}H_{25}NO_2^+$: [M$^+$], |Δmu = 0.5|).

Imine 11b: $R_f = 0.23$ (silica gel, dichloromethane). ^{1}H NMR (300 MHz, $CDCl_3$, room temp.): δ = 1.63 (d, *J* = 7.3 Hz, 3 H), 1.71 (s, br.), 1 H), 2.24 (s, 3 H), 3.90 (ψd, *J* = 6.6 Hz, 2 H), 4.44 (ψt, *J* = 6.6 Hz, 1 H), 4.67 (q, *J* = 7.3 Hz, 1 H), 6.94 (d, *J* = 1.1 Hz, 1 H), 6.99 (d, *J* = 1.1 Hz, 1 H), 7.15−7.21 (m, 1 H), 7.27−7.33 (m, 5 H), 7.36−7.41 (m, 4 H), 8.44 (s, 1 H), 13.26 (s, br.), 1 H) ppm. ^{13}C{^{1}H} NMR (75 Hz, $CDCl_3$, room temp.): δ = 20.5, 20.7, 36.8, 67.7, 75.7, 118.0, 125.8, 127.2, 127.5, 127.7, 127.8, 128.2, 128.8,.129.8, 132.1, 134.1, 139.3, 145.8. 156.1, 166.7 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3584 cm^{-1}, 3462, 3083, 3060, 3026, 2965, 2928, 2872, 1628, 1600, 1493, 1456, 1452, 1262, 1238, 699. HRMS *m*/*z* = 359.1879 (69.4%, M$^+$, $C_{24}H_{25}NO_2^+$:[M$^+$], |Δmu = 0.6|).

(*S*)-2-Hydroxy-5-methyl-3-(1-phenylethyl)benzaldehyde (6): Hydrochloric acid (5 mL, 10%) was added to a solution of the imine **11a** (3.05 g, 8.49 mmol) in methanol (15 mL). The mixture was heated under reflux for 1 h, and the solvent was removed under reduced pressure. The residue was diluted with 20 mL of water and extracted with dichloromethane (5 × 30 mL). The organic layer was dried over sodium sulfate, and the solvent was removed under reduced pressure. After chromatography (silica gel, dichloromethane) of the crude product, followed by kugelrohr distillation (155 °C, 0.23 mbar), the enantiomerically pure aldehyde **6** (1.98 g, 8.24 mmol, 97%) was obtained as a colorless solid. m.p. 30 °C. $[\alpha]_D^{20}$ = +167.1, $[\alpha]_{578}$ = +178.2, $[\alpha]_{546}$ = +214.8, $[\alpha]_{436}$ = +579.1 (*c* = 0.93, chloroform). $C_{16}H_{16}O_2$ (240.30): calcd. C 79.96, H 6.72; found C 80.21, H 6.68.

The enantiomeric purities of the salicylic aldehydes **6** and *ent*-**6** were established by analytical HPLC (Chiralcel OD-H; *n*-hexane/2-propanol, 200:1, 1 mL/min).

(*R*)-2-Hydroxy-5-methyl-3-(1-phenylethyl)benzaldehyde (*ent*-6): Analogously to the preparation of **6,** the imine **11b** (1.55 g, 4.32 mmol) was hydrolyzed to provide the enantiomerically pure aldehyde *ent*-**6** (985 mg, 4.10 mmol, 98%). m.p. 29−30 °C. $[\alpha]_D^{20}$ = 65.2, $[\alpha]_{578}$ = −176.8, $[\alpha]_{546}$ = −212.6, $[\alpha]_{436}$ = −573.3 (*c* = 0.90, chloroform). $C_{16}H_{16}O_2$ (240.30): calcd. C 79.96, H 6.72; found C 79.73, H 6.52.

[*S*-[*R*,*R*-(*E*)]]-2-{[[2-Hydroxy-5-methyl-3-(1-phenyethyl)phenyl]-methylene]amino}-3-methylbutaneamide (12): The salicylic aldehyde **6** (195 mg, 811 μmol) was added at room temperature to a solution of L-valinamide hydrochloride (123 mg, 811 μmol) and potassium hydroxide (45.5 mg, 811 μmol) in methanol (15 mL). Molecular sieves (4 Å, 8 mg) were added and the mixture was shaken at room temperature for 12 h. After filtration, the solvent was removed under reduced pressure. The residue was taken up in chloroform (20 mL). The mixture was filtered and the solvent was removed under reduced pressure, affording the crude imine **12** (270 mg, 798 μmol, 98%) as a yellow solid. An analytical sample was recrystallized from chloroform/*n*-hexane. $R_f = 0.74$ (silica gel, ethyl acetate); m.p. 160 °C (chloroform/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$, room temp.): δ = 0.94 (d, *J* = 7.0 Hz, 3 H), 1.02 (d, *J* = 7.0 Hz, 3 H), 1.61 (d, *J* = 7.0 Hz, 3 H), 2.28 (s, 3 H), 2.35−2.53 (m, 1 H), 3.67 (d, *J* = 4.0 Hz, 1 H), 4.64 (q, *J* = 7.0 Hz, 1 H), 5.47 (s, br.), 1 H), 6.01 (s, br.), 1 H), 6.95−7.40 (m, 7 H), 8.26 (s, 1 H), 12.54 (s, br.), 1 H) ppm. ^{13}C{^{1}H} NMR (75 Hz, $CDCl_3$, room temp.): δ = 17.3, 19.6, 20.5, 21.0, 32.1, 36.8, 79.5, 117.6, 125.9, 127.7, 128.0, 128.3, 130.2, 132.4, 134.0, 145.8, 155.8, 168.1, 173.6 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3471 cm^{-1}, 3230, 3100, 2963, 2870, 1694, 1662, 1628, 1591, 1458, 1368, 705. $C_{21}H_{26}N_2O_2$ (338.44): calcd. C 74.53, H 7.74, N 8.28; found C 74.25, H 7.73, N 8.13.

(1*S*-*exo*)- and (1*R*-*exo*)-4-Methyl-2-(1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl)phenol (*rac*-15) and [1*S*-(2*exo*,6*exo*)]- and [1*R*-(2*exo*,6*exo*)]-4-Methyl-2-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)-phenol (*rac*-16): (+)-Camphene (**14**, 10.4 g, 76.5 mmol, 1.00 equiv.) was added dropwise under nitrogen, over a period of 4 h, to a refluxing solution of *p*-cresol (**13**, 16.5 g, 153 mmol, 2.00 equiv.) and conc. sulfuric acid (1.50 g, 15.3 mmol, 0.20 equiv.) in toluene (25 mL). The mixture was heated under reflux for an additional 6 h. After the mixture had cooled to room temperature, water (100 mL) was added. The organic layer was extracted with diethyl ether (4 × 100 mL). The extract was dried over sodium sulfate and the solvent was removed under reduced pressure. After chromatography (silica gel, toluene) of the crude product, followed by kugelrohr distillation (170 °C, 0.40 mbar), a mixture of the isomers *rac*-**15** and *rac*-**16** (10.3 g, 42.2 mmol, 55%) was obtained (HPLC: *rac*-**15**/*rac*-**16** = 1.0:1.0). Separation of 8.50 g (34.8 mmol) of this mixture by preparative HPLC (LiChrosorb® Si-60, dichloromethane/2-propanol, 500:1, 80 mL/min) afforded *rac*-**15** (4.20 g, 17.2 mmol, 49%) and *rac*-**16** (3.43 g, 14.5 mmol, 40%) as colorless oils, both of which crystallized after several days. Both racemic mixtures *rac*-**15** and *rac*-**16** were separated by preparative chiral HPLC (Chiralcel® OJ, heptane/2-propanol, 80:20). The separation of 2.20 g (9.00 mmol) of *rac*-**15** afforded **15** (1.01 g, 4.13 mmol, 46%, >99.5% *ee*) and *ent*-**15** (950 mg, 3.89 mmol, 43%, >99.5% *ee*). The separation of 2.12 g (8.69 mmol) of *rac*-**16** afforded **16** (820 mg, 3.36 mmol, 39%, 99% *ee*) and *ent*-**16** (790 mg, 3.23 mmol, 37%, >99% *ee*).

Racemate *rac*-15: $R_f = 0.45$ (silica gel, toluene); m.p. 63 °C. ^{1}H NMR (300 MHz, $CDCl_3$, room temp.): δ = 0.80 (s, 3 H), 0.85 (s,

3 H), 0.91 (s, 3 H), 1.31−1.49 (m, 2 H), 1.56−1.69 (m, 2 H), 1.83−1.92 (m, 2 H), 2.18−2.36 (m, 1 H), 2.37 (s, 3 H), 3.10 (ψt, J = 8.8 Hz, 1 H), 4.56 (s, 1 H), 6.66 (d, J = 8.0 Hz, 1 H), 6.86 (dd, J = 8.0, J = 1.2, 1 H), 7.11 (d, J = 1.2 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 Hz, $CDCl_3$, room temp.): δ = 12.3, 20.3, 21.0, 21.5, 27.6, 33.9, 40.0, 45.5, 45.6, 48.1, 49.8, 114.8, 126.8, 128.9, 129.2, 129.3, 152.5 ppm. IR (KBr pellet): ṽ = 3314 cm^{-1}, 3020, 2952, 2931, 2875, 1609, 1506, 1491, 1246, 1201, 808. $C_{17}H_{24}O$ (244.37): calcd. C 83.55, H 9.90; found C 83.38, H 9.91.

Enantiomer 15: M.p. 43 °C. $[\alpha]_D^{20}$ = 59.9, $[\alpha]_{578}$ = −62.6, $[\alpha]_{546}$ = −71.7, $[\alpha]_{436}$ = −122.8 (c = 0.45, chloroform). $C_{17}H_{24}O$ (244.37): calcd. C 83.55, H 9.90; found C 83.25, H 9.89.

The enantiomeric purities of the phenols **15** and *ent*-**15** were established by analytical HPLC (Chiralcel OJ; *n*-heptane/2-propanol, 80:20, 0.8 mL/min; or Chiralcel OD-H; *n*-hexane/2-propanol, 99:1, 1 mL/min).

Enantiomer *ent*-15: M.p. 43 °C. $[\alpha]_D^{20}$ = +60.5, $[\alpha]_{578}$ = +63.2, $[\alpha]_{546}$ = +72.3, $[\alpha]_{436}$ = +123.7 (c = 0.62, chloroform). $C_{17}H_{24}O$ (244.37): calcd. C 83.55, H 9.90; found C 83.26, H 10.04.

Racemate *rac*-16: R_f = 0.42 (silica gel, toluene); m.p. 40 °C. ^1H NMR (300 MHz, $CDCl_3$, room temp.): δ = 0.93−0.97 (m, 6 H), 1.04 (s, 3 H), 1.32−1.43 (m, 3 H), 1.71−1.76 (m, 1 H), 1.77−1.83 (m, 1 H), 1.96−1.99 (m, 1 H), 2.21-2-32 (m, 1 H), 2.26 (s, 3 H), 2.79−2.87 (m, 1 H), 4.54 (s, 1 H), 6.67 (d, J = 8.0 Hz, 1 H), 6.84 (dd, J = 8.0, J = 2.1, 1 H), 6.96 (d, J = 2.1 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 Hz, $CDCl_3$, room temp.): δ = 16.3, 20.8, 24.8, 27.7, 32.5, 33.5, 39.6, 40.6, 48.9, 49.8, 50.8, 115.0, 126.4, 126.8, 129.5, 132.7, 151.1 ppm. IR (KBr pellet): ṽ = 3288 cm^{-1}, 3027, 2960, 2930, 2889, 2866, 1610, 1508, 1491, 1254, 1205, 807. $C_{17}H_{24}O$ (244.37): calcd. C 83.55, H 9.90; found C 83.34, H 9.66.

Enantiomer 16: $[\alpha]_D^{20}$ = 42.9, $[\alpha]_{578}$ = −45.2, $[\alpha]_{546}$ = −51.5, $[\alpha]_{436}$ = −88.8 (c = 0.72, chloroform). $C_{17}H_{24}O$ (244.37): calcd. C 83.55, H 9.90; found C 83.31, H 9.87.

The enantiomeric purities of the phenols **16** and *ent*-**16** were established by analytical HPLC (Chiralcel OJ; *n*-heptane/2-propanol, 80:20, 0.8 mL/min; or Chiralcel OD-H; *n*-hexane/2-propanol, 99:1, 1 mL/min).

Enantiomer *ent*-16: $[\alpha]_D^{20}$ = +42.3, $[\alpha]_{578}$ = +44.5, $[\alpha]_{546}$ = +50.9, $[\alpha]_{436}$ = +87.8 (c = 0.65, chloroform). $C_{17}H_{24}O$ (244.37): calcd. C 83.55, H 9.90; found C 83.42, H 9.92.

(1*S*-*exo*)-1-Bromo-5-methyl-3-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)phenol (*ent*-17): A solution of bromine (65.4 mg, 409 mmol) in tetrachloromethane (1 mL) was added dropwise at 0 °C to a solution of *ent*-**15** (100 mg, 409 mmol) in tetrachloromethane (1 mL). After final decoloration, the mixture was washed with 2 mL of a saturated solution of sodium thiosulfate and with 2 mL of water. The organic layer was dried with sodium sulfate and the solvent was removed under reduced pressure to afford *ent*-**17** (117 mg, 362 mmol, 89%) as colorless crystals. For analytic purposes, a sample of *ent*-**17** was sublimed (75 °C, 0.1 mbar). R_f = 0.75 (silica gel, toluene); m.p. 95 °C. ^1H NMR (300 MHz, $CDCl_3$, room temp.): δ = 0.77 (s, 3 H), 0.84 (s, 3 H), 0.87 (s, 3 H), 1.22−1.40 (m, 2 H), 1.41−1.68 (m, 2 H), 1.76−1.92 (m, 2 H), 2.07−2.20 (m, 1 H), 2.25 (s, 3 H), 3.25 (t, J = 9.1 Hz, 1 H), 5.46 (s, 1 H), 7.04 (s, 1 H), 7.09 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 Hz, $CDCl_3$, room temp.): δ = 12.2, 20.3, 20.7, 21.4, 27.4, 34.0, 39.6, 45.6, 46.0, 48.0, 50.1, 110.1, 128.5, 128.9, 129.9, 131.4, 148.9 ppm. IR (KBr): ṽ = 3511 cm^{-1}, 3022, 2948, 2876, 1472, 1465, 1235, 1190, 844, 767. $[\alpha]_D^{20}$ = +8.6 (c = 1.00, chloroform). $C_{17}H_{23}OBr$ (323.27): calcd. C 63.16, H 7.17; found C 62.89, H 7.06.

(1*RS*-*exo*)-2-Hydroxy-5-methyl-3-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)benzaldehyde (*rac*-7): Tin(IV)chloride (96.5 μL, 820 μmol, 0.10 equiv.) and paraformaldehyde (491 mg, 16.4 mmol, 2.00 equiv.) were added in small portions at room temperature to a solution of the phenol *rac*-**15** (2.00 g, 8.18 mmol, 1.00 equiv.) and tri-*n*-butylamine (778 μL, 3.27 mmol, 0.40 equiv.) in toluene (12 mL). The mixture was heated under reflux under nitrogen for 10 h. After cooling to room temperature, the solution was added to 200 mL of water and acidified to pH 2 with hydrochloric acid (10%). The aqueous layer was extracted with toluene (3 × 100 mL). The extract was dried over sodium sulfate and the solvent was removed under reduced pressure. Purification of the crude product by chromatography (silica gel, toluene) afforded the desired aldehyde *rac*-**7** (1.59 g, 5.83 mmol, 71%) as colorless crystals. R_f = 0.65 (silica gel, toluene); m.p. 103 °C (methanol). ^1H NMR (300 MHz, $CDCl_3$, room temp.): δ = 0.74 (s, 3 H), 0.82 (s, 3 H), 0.85 (s, 3 H), 1.29−1.43 (m, 1 H), 1.47−1.66 (m, 3 H), 1.79−1.92 (m, 2 H), 2.08−2.20 (m, 1 H), 2.33 (s, 3 H), 3.31 (ψt, J = 9.0 Hz, 1 H), 7.15 (d, J = 1.2 Hz, 1 H), 7.37 (d, J = 1.2 Hz, 1 H), 9.83 (s, 1 H), 11.36 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 Hz, $CDCl_3$, room temp.): δ = 12.2, 20.3, 20.7, 21.4, 27.4, 33.8, 39.6, 44.2, 45.7, 48.1, 50.0, 119.7, 127.8, 130.7, 132.6, 136.6, 159.2, 196.8 ppm. IR (KBr pellet): ṽ = 3600−3300 cm^{-1}, 3000, 2950, 2877, 2844, 1653, 1617, 1600, 1476, 1259, 1243, 746. HRMS m/z = 272.1774 (1.9%, M^+, $C_{18}H_{24}O_2^+$: [M^+], |Δmu = 0.3|).

[1*S*-[2*exo*(*S)]]- and [1*R*-[2*exo*(*R**)]-β-{[[2-Hydroxy-5-methyl-3-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)phenyl]methylene]amino}-phenylethanol (18a and 18b):** A solution of the aldehyde *rac*-**7** (272 mg, 1.00 mmol, 1.00 equiv.) and (*R*)-phenylglycinol **10** (151 mg, 1.10 mmol, 1.10 equiv.) in methanol (10 mL) was stirred for 3 days at room temperature. The solvent was removed under reduced pressure. The crude product was purified by chromatography (silica gel, dichloromethane, 2-propanol; 100:1). The resulting mixture of diastereomers **18a** and **18b** was separated by preparative HPLC (LiChrosorb® Si-60; dichloromethane, 2-propanol, 600:1, 80 mL/min) to provide the imines **18a** (148 mg, 378 μmol, 38%, >99% *de*) and **18b** (165 mg, 421 μmol, 42%, >99% *de*) as yellow solids.

Compound 18a: R_f = 0.33 (silica gel, dichloromethane); m.p. 58−59 °C. ^1H NMR (300 MHz, $CDCl_3$, room temp.): δ = 0.81 (s, 3 H), 0.84 (s, 3 H), 0.91 (s, 3 H), 1.31−1.41 (m, 1 H), 1.53−1.64 (m, 3 H), 1.80−1.85 (m, 3 H), 2.05−2.18 (m, 1 H), 2.27 (s, 3 H), 3.35 (ψt, J = 9.0 Hz, 1 H), 3.84−3.98 (m, 2 H), 4.46 (dd, J = 7.7, J = 5.4, 1 H), 6.88 (d, J = 1.1 Hz, 1 H), 7.18 (d, J = 1.1 Hz, 1 H), 2.27−7.40 (m, 5 H), 8.42 (s, 1 H), 13.41 (s, br.), 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 Hz, $CDCl_3$, room temp.): δ = 12.3, 20.3, 20.6, 21.2, 27.3, 34.0, 39.6, 44.3, 45.5, 47.8, 49.7, 67.6,.75.5, 117.3, 126.4, 127.0, 127.6, 128.6, 129.0, 131.5, 132.2, 139.3, 157.9, 166.8 ppm. IR (KBr pellet): ṽ = 3422 cm^{-1}, 2052, 3025, 2950, 2875, 1628, 1598, 1491, 1454, 1258, 700. HRMS m/z = 391.2476 (100.0%, M^+, $C_{26}H_{33}NO_2^+$:[M^+], |Δmu = 3.6|).

The diastereomeric purities of the imines **18a** and **18b** were established by analytical HPLC (LiChrosorb® Si-60; dichloromethane/2-propanol, 200:1, 1 mL/min).

Compound 18b: R_f = 0.33 (silica gel, dichloromethane); m.p. 59 °C. ^1H NMR (300 MHz, $CDCl_3$, room temp.): δ = 0.77 (s, 3 H), 0.83 (s, 3 H), 0.89 (s, 3 H), 1.31−1.42 (m, 1 H), 1.51−1.65 (m, 3 H), 1.80−1.84 (m, 3 H), 2.07−2.17 (m, 1 H), 2.27 (s, 3 H), 3.33 (ψt, J = 9.0 Hz, 1 H), 3.87 (ψd, J = 6.6 Hz, 2 H), 4.46 (ψt, J = 6.6 Hz,

1 H), 6.89 (d, J = 1.1 Hz, 1 H), 7.18 (d, J = 1.1 Hz, 1 H), 2.25−7.43 (m, 5 H), 8.42 (s, 1 H), 13.36 (s, br.), 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 Hz, $CDCl_3$, room temp.): δ = 12.2, 20.3, 20.6, 21.2, 27.3, 34.0, 39.6, 44.4, 45.5, 47.8, 49.7, 67.6, 75.6, 117.3, 126.4, 126.9, 127.6, 128.6, 128.9, 131.5, 132.1, 139.3, 157.9, 166.7 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3408 cm^{-1}, 3052, 3026, 2951, 2875, 1629, 1598, 1491, 1454, 1259, 700. HRMS m/z = 391.2519 (100.0%, M^+, $C_{26}H_{33}NO_2^+$: [M^+], |Δmu = 0.8|).

(1*S*-*exo*)-2-Hydroxy-5-methyl-3-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)benzaldehyde (7): Hydrochloric acid (2 mL, 32%) was added to a solution of the imine **18a** (148 mg, 378 μmol) in ethanol (3 mL). The mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue was partitioned between 10 mL water and 75 mL of dichloromethane. The organic layer was dried over sodium sulfate, and the solvent was removed under reduced pressure. Chromatography (silica gel, dichloromethane) of the crude product afforded the enantiomerically pure aldehyde **7** (80.0 mg, 294 μmol, 78%) as a colorless solid. m.p. 109 °C (methanol). $[\alpha]_D^{20}$ = +42.7, $[\alpha]_{578}$ = +46.7, $[\alpha]_{546}$ = +62.8, $[\alpha]_{436}$ = +281.7 (c = 0.30, chloroform). $C_{18}H_{24}O_2$ (272.38): calcd. C 79.37, H 8.88; found C 79.08, H 8.95.

The enantiomeric purities of the salicylic aldehydes **7** and *ent*-**7** were established by analytical HPLC (Chiralcel OD-H; *n*-hexane/2-propanol, 200:1, 0.25 mL/min).

(1*R*-*exo*)-2-Hydroxy-5-methyl-3-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)benzaldehyde (*ent*-7): As in the preparation of **7**, imine **18b** (165 mg, 421 μmol) was hydrolyzed to provide the enantiomerically pure aldehyde *ent*-**7** (100 mg, 367 μmol, 87%). m.p. 108−109 °C (methanol). $[\alpha]_D^{20}$ = 42.3, $[\alpha]_{578}$ = −46.2, $[\alpha]_{546}$ = −62.2, $[\alpha]_{436}$ = −279.9 (c = 0.07, chloroform). $C_{18}H_{24}O_2$ (272.38): calcd. C 79.37, H 8.88; found C 79.36, H 8.69.

(1*S*-*exo*)-2-Hydroxy-5-methyl-3-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)benzaldehyde (7): Analogously to the preparation of the aldehyde *rac*-**7** from the phenol *rac*-**15** (vide supra), phenol **15** (99.0%*ee*, 300 mg, 1.23 mmol) was formylated to afford the enantiomerically pure aldehyde **7** (50.0 mg, 184 μmol, 15%). $[\alpha]_D^{20}$ = +35.3, $[\alpha]_{578}$ = +38.4, $[\alpha]_{546}$ = +52.3, $[\alpha]_{436}$ = +232.1 (c = 0.52, chloroform). $C_{18}H_{24}O_2$ (272.38): calcd. C 79.37, H 8.88; found C 79.31, H 8.84.

(1*R*-*exo*)-2-Hydroxy-5-methyl-3-(1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl)benzaldehyde (*ent*-7): Analogously to the preparation of the aldehyde *rac*-**7** from the phenol *rac*-**15** (vide supra), phenol *ent*-**15** (98.6% *ee*, 226 mg, 925 μmol) was formylated to afford the enantiomerically pure aldehyde *ent*-**7** (104 mg, 382 μmol, 41%). $[\alpha]_D^{20}$ = 34.9, $[\alpha]_{578}$ = −37.8, $[\alpha]_{546}$ = −51.1, $[\alpha]_{436}$ = −227.1 (c = 0.50, chloroform). $C_{18}H_{24}O_2$ (272.38): calcd. C 79.37, H 8.88; found C 79.37, H 8.84.

[1*RS*-(2*exo*,6*exo*)]-2-Hydroxy-5-methyl-3-(5,5,6-trimethylbicyclo-[2.2.1]hept-2-yl)benzaldehyde (*rac*-8): Analogously to the preparation of salicylic aldehyde *rac*-**7** from the phenol *rac*-**15** (vide supra), the phenol *rac*-**16** (2.00 g, 8.18 mmol) was formylated to afford the aldehyde *rac*-**8** (1.85 g, 6.79 mmol, 83%). R_f = 0.64 (silica gel, toluene). ^1H NMR (300 MHz, $CDCl_3$, room temp.): δ = 0.88−0.94 (m, 6 H), 1.07 (s, 3 H), 1.25−1.44 (m, 3 H), 1.72−1.77 (m, 1 H), 1.77−1.82 (m, 1 H), 1.90−1.95 (m, 1 H), 2.24−2.32 (m, 1 H), 2.32 (s, 3 H), 3.00−3.08 (m, 1 H), 7.14 (d, J = 1.2 Hz, 1 H), 7.24 (d, J = 1.2 Hz, 1 H), 9.82 (s, 1 H), 11.22 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, room temp.): δ = 16.3, 20.6, 24.8, 27.6, 32.6, 33.6, 39.6, 39.9, 48.8, 49.8, 50.8, 119.0, 128.2, 130.2, 134.2, 135.9, 157.8, 196.8 ppm. IR (NaCl, film): $\tilde{\nu}$ = 3600−3100 cm^{-1} (br.), 3010, 2950, 2873, 2840, 1650, 1618, 1604, 1451, 1262, 1249, 731.

[1*S*-(2*exo*,6*exo*)]-2-Hydroxy-5-methyl-3-(5,5,6-trimethylbicyclo-[2.2.1]hept-2-yl)benzaldehyde (8): Analogously to the preparation of salicylic aldehyde *rac*-**7** from the phenol *rac*-**15** (vide supra), the phenol **16** (300 mg, 1.23 mmol) was formylated to afford the aldehyde **8** (50.0 mg, 184 μmol, 15%). $[\alpha]_{589}$ = +35.3, $[\alpha]_{578}$ = +38.4, $[\alpha]_{546}$ = +52.3, $[\alpha]_{436}$ = +232.1 (c = 0.52, chloroform). $C_{18}H_{24}O_2$ (272.38): calcd. C 79.37, H 8.88; found C 79.31, H 8.84.

[1*R*-(2*exo*,6*exo*)]-2-Hydroxy-5-methyl-3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)benzaldehyde (*ent*-8): Analogously to the pre-

Table 1. Experimental parameters of the X-ray structural analyses of *rac*-**15**, *rac*-**16**, **12**, and *ent*-**17**.

Entry	*rac*-**15**	*rac*-**16**	**12**	*ent*-**17**
Formula	$C_{17}H_{24}O$	$C_{17}H_{24}O$	$C_{21}H_{26}N_2O_2$	$C_{17}H_{23}OBr$
M_r	244.36	244.36	338.44	323.26
Crystal dimensions [mm]	0.25 × 0.10 × 0.10	0.15 × 0.10 × 0.10	0.20 × 0.15 × 0.15	0.15 × 0.15 × 0.15
Crystal system	Triclinic	Triclinic	Monoclinic	Orthorhombic
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1$	$P2_12_12_1$
a [Å]	11.216(1)	9.454(1)	8.288(1)	7.908(1)
b [Å]	11.291(1)	12.036(1)	7.943(1)	13.881(1)
c [Å]	14.435(1)	14.537(1)	14.798(1)	14.128(1)
α [°]	111.27(1)	106.56(1)	90	90
β [°]	94.82(1)	106.88(1)	95.90(1)	90
γ [°]	115.96(1)	94.45(1)	90	90
V [Å^3]	1465.9(2)	1493.9(5)	969.0(2)	1550.8(3)
$\rho_{calcd.}$ [gcm^{-3}]	1.107	1.087	1.160	1.385
Z	4	4	2	4
Radiation	Mo-K_α	Mo-K_α	Mo-K_α	Mo-K_α
Scan mode	φ/ω	φ/ω	φ/ω	φ/ω
2 Θ_{max} [°]	54	54	54	54
Unique reflections	6391	6491	4038	3323
Observed reflections [$I > 2\sigma(I)$]	4424	2772	3320	2686
R (F)	0.0574	0.1220	0.0429	0.0342
$R_w(F^2)$	0.1360	0.2872	0.1015	0.0746
$\rho_{fin.}$ (max) [e·Å^{-3}]	0.185	0.304	0.138	0.182
CCDC deposition no.	185866	185867	185868	185869

paration of salicylic aldehyde *rac*-**7** from the phenol *rac*-**15** (vide supra), the phenol *ent*-**16** (226 mg, 925 μmol) was formylated to afford the aldehyde *ent*-**8** (104 mg, 382 μmol, 41%). $[\alpha]_{589} = -34.9$, $[\alpha]_{578} = -37.8$, $[\alpha]_{546} = -51.1$, $[\alpha]_{436} = -227.1$ ($c = 0.50$, chloroform). $C_{18}H_{24}O_2$ (272.38): calcd. C 79.37, H 8.88; found C 79.31, H 8.84.

X-ray Structure Determination of *rac*-15, *rac*-16, 12, and *ent*-17: Crystals suitable for X-ray structural analyses were obtained in the following ways: *rac*-**15**, *rac*-**16**: crystallization of the purified materials (oils) without added solvent. **12**: crystallization from *n*-hexane/chloroform; *ent*-**17**: sublimation at 75 °C, 0.1 mbar.

CCDC-numbers in Table 1 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

This work was supported by the Fonds der Chemischen Industrie and in part by the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 247 and Graduiertenkolleg "Selectivity in Organic and Metal-Organic Synthesis and Catalysis"). The authors thank Dr. A. H. Vetter for synthetic support.

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Received March 4, 2002
[O02114]